Investigation and application of boron-BINOL catalysed asymmetric aza Diels-Alder reactions

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Investigation and Application of Boron-BINOL Catalysed Asymmetric Aza Diels-Alder Reactions

Michael James Thatcher

A thesis submitted for the degree of Doctor of Philosophy

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Finally, thanks must go out to my Dad, Mom and brother Dave for their help, support and belief in me.

Abbreviations

Å	Angstrom
Ac	Acetyl
acac	Acetylacetone
AIBN	Azobis(isobutyronitrile)
AN	Acceptor number
aq.	Aqueous
Ar	Aromatic
BANOL	10,10'-Dihydroxy-9,9-biphenanthryl
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
BINOL	1,1'-Bi-2-naphthol
BLA	Brønsted acid-assisted chiral Lewis acid
Boc	^{t}Butyloxycarbonyl
$B(OMe)_3$	Trimethylborate
Bn	Benzyl
br	Broad
Bu	Butyl
^{i}Bu	*iso*-Butyl
^{n}Bu	*normal*-butyl
^{s}Bu	*sec*-Butyl
^{t}Bu	*tert*-Butyl
^{n}BuLi	*n*-Butyllithium
°C	Degrees celcius
CA	Chiral auxilary
CAB	Chiral(acyloxyborane)
CAN	Ceric ammonium nitrate
cat.	Catalytic quantity
CBS	Corey-Bakshi-Shibata catalyst
CDA	Chiral derivatising agent
CH	1,3-cyclohexadiene
CI	Chemical ionization
cm	Centimetre
conc.	Concentrated

Cp	Cyclopentadiene
cy	Cyclohexyl
δ	Chemical shift in parts per million
d	Doublet
Danishefsky's Diene	1-Methoxy-3-trimethylsiloxybuta-1,3-diene
DBU	1,8-Diazobicyclo[5.4.0]undec-7-ene
dd	Doublet of doublet
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
ddt	Doublet of doublet of triplets
de	Diastereomeric excess
DEAD	Diethyl azodicarboxylate
dec.	Decomposition
DET	Diethyl tartrate
dil.	Diluted
DMAP	4-Dimethylaminiopyridine
DMF	*N,N'*-Diemthylformamide
DMP	2,6-Dimethyl pyridine
DMS	Dimethyl sulfide
DMSO	Dimethyl sulfoxide
DMBMP	2,6-Di-*tert*-butyl-4-methyl pyridine
dt	Doublet of triplets
DTBP	2,6-Di-*tert*-butyl pyridine
ee	Enantiomeric excess
EI	Electron impact
eq.	Equivalent
ES	Electrospray
Et	Ethyl
EtOAc	Ethyl acetate
g	Gram
h	Hour
hept	Heptuplet
HPLC	High performance liquid chromatography
HOMO	Highest occupied molecular orbital
HRMS	High resolution mass spectrometry

Hz	Hertz
Ip	Isoprene
IPc_2BH	Bisisopinocampheylborane
IPA	*iso*-propyl alcohol
IR	Infrared
J	Coupling constant
L	Ligand
LA	Lewis acid
LDA	Lithium diisopropylamide
LLA	Lewis acid-assisted Lewis acid
LUMO	Lowest unoccupied molecular orbital
M	Molar
m	Multiplet
m	*meta*
Me	Methyl
mg	Milligram
MHz	Megahertz
min	Minute
ml	Millilitre
mmol	Millimole
MOM	Methoxy methyl
Mosher's reagent	α-Methoxy-trifluromethylphenylacetic acid
mp	Melting point
MS	Molecular sieves, mass spectroscopy
Ms	Methanesulfonyl
MTPA	α-Methoxy-trifluromethylphenylacetic acid (Mosher's reagent)
MW	Molecular weight
m/z	Mass to charge ratio
n	*normal*
nm	Nanometre
NMI	*N*-Methylimidazole
σ	*ortho*
ORTEP	Oak Ridge thermal eclipse programme
p	*para*

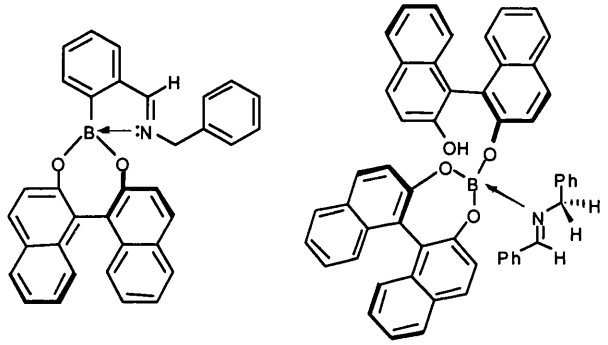
Petrol	Petroleum ether
Pf	Heptadecafluorooctane sulfonate
Ph	Phenyl
ppm	Parts per million
Pr	Propyl
^{i}Pr	*iso*-Propyl
^{n}Pr	*normal*-Propyl
Py	Pyridine, pyridyl
q	Quartet
quin	Quintet
R	Generic substrate
Rac	Racemic
rt	Room temperature
s	Singlet
sat.	Saturated
sol.	Solution
t	Triplet
td	Triplet of doublets
TBAF	Tetrabutylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
TES	Triethylsilyl
TFA	Trifluoroacetic acid
Tf	Trifluoromethylsulfonyl
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TLC	Thin layer chromatography
TMEDA	*N,N,N,N*'-Tetramethylethylenediamine
TMS	Trimethylsilyl, tetramethylsilane
Tol	*p*-Tolyl
Ts	*p*-toluenesulfonyl (tosyl)
VANOL	3,3'-Diphenyl-(2,2'-binaphthalene)-1,1'-diol
VAPOL	2,2'-Diphenyl-(3,3'-biphenanthrene)-4,4'-diol
X	Generic halide substituent
ν	Wavenumber

Abstract

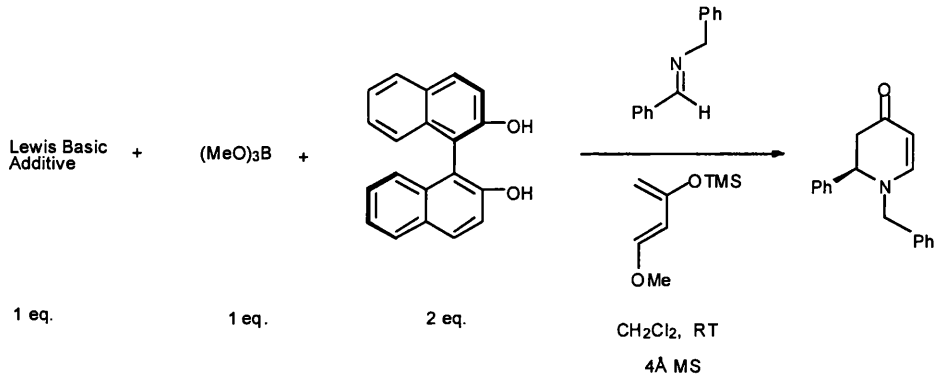
The aza Diels-Alder reaction is potentially of great importance given the abundance of 6-membered nitrogen containing natural products that have been isolated. Currently, there are only a handful of effective methodologies for the asymmetric aza Diels-Alder reaction of imines. This thesis describes my investigations of boron-BINOL asymmetric catalysts and their application for the aza Diels-Alder reaction.

The first chapter reviews the current methods employed for the aza Diels-Alder reaction and the use of boron Lewis acid catalysts for various asymmetric transformations.

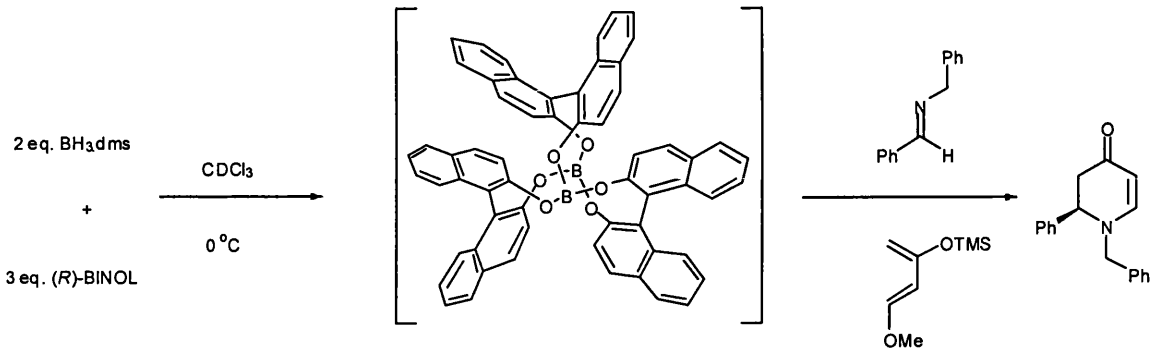
The second chapter explains our investigations into the structure and activity of boron-BINOL catalyst, and the synthesis of stable boronates designed to replicate these boron-BINOL catalysts.



The third chapter describes our optimisations of the boron-BINOL catalysed aza Diels-Alder reaction, concentrating on strategies that increase enantioselectivity at room temperature.

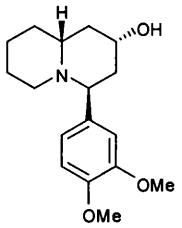


The fourth chapter describes how a C_3-symmetric propeller boronate based on BINOL could be used as a successful boron-BINOL catalyst for the asymmetric aza Diels-Alder reaction of imines, with moderate to high enantioselectivities obtained when the reaction is carried out at room temperature and – 78 °C.

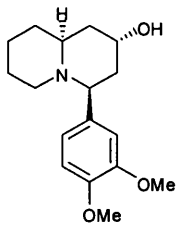


The fifth chapter shows how the boron-BINOL catalysed aza Diels-Alder reaction can be employed with a significant number of substrates. The boron-BINOL catalyst was also shown to catalyse other reaction types.

Finally, the sixth chapter describes how the boron-BINOL catalysed aza Diels-Alder reaction was successfully employed as part of a natural product synthesis. Lasubine (I) and Lasubine (II) were both synthesised using an asymmetric aza Diels-Alder reaction as the key synthetic step.



(-)-Lasubine I



(-)-Lasubine II

Contents

1 Introduction

1.1 General Introduction

This research thesis describes the use of boron-BINOL catalysts for the asymmetric aza Diels-Alder reaction. Consequently, this chapter introduces the theme of chirality and asymmetric synthesis, followed by a review of enantioselective Diels-Alder reactions of imines. Finally the application of asymmetric boron catalysts and reagents are reviewed to set the scene for the results and discussion section.

1.2 Chirality

The property of molecules existing in left and right handed structural forms is known as chirality. These molecules, which are non-superimposable on their mirror image, may appear to be identical in terms of their physical properties, but can actually have markedly different properties when interacting with other chiral molecules in biological systems. An example of such a phenomenon in nature is the two enantiomers of limonene, whereby each of the two enantiomers interacts with nasal receptors in different ways. *R*-(+)-limonene **1** smells of oranges whilst *S*-(-)-limonene **2** smells of lemon (Figure 1).

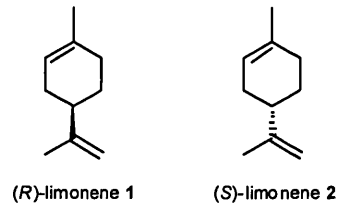
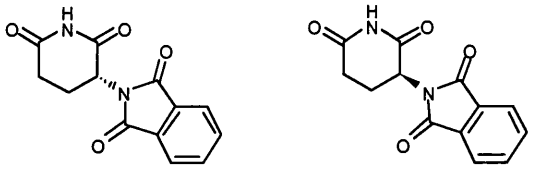


Figure 1: The two enantiomers of limonene.

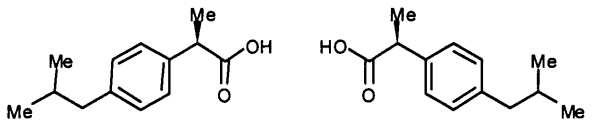
Chirality is now fundamentally important to the pharmaceutical industry, with chiral drugs representing a multi-billion dollar industry. Chiral drugs are often sold in the racemic form (racemate), with the biological activity resulting from just one enantiomer. In the 1960's the drug thalidomide was prescribed to pregnant women to help reduce morning sickness (Figure 2). Unfortunately the drug contained both enantiomers of thalidomide and with tragic consequences it was later found that while the (*R*)-enantiomer **3** was effective, metabolites of the (*S*)-enantiomer **4** damaged the foetus.[1] This case indicates the importance of synthesising a drug as a single enantiomer.



(*R*)-(+)-thalidomide **3** (*S*)-(+)-thalidomide **4**

Figure 2: The 1960's drug thalidomide was prescribed as a racemic mixture.

Another example where a drug is sold as a racemic mixture is the well known pain-relief drug ibuprofen (Figure 3). In this example the compounds biological activity can be attributed to the (*S*)-enantiomer **6**. The (*R*)-enantiomer **5** exhibits no known side effects hence an asymmetric synthesis is not carried out due to cost.[2] It is the ongoing aim of research within the field of asymmetric synthesis which will allow for the synthesis of different classes of drug in their enantiopure form.



(*R*)-ibuprofen **5** (*S*)-ibuprofen **6**

Figure 3: The (*S*)-enantiomer of ibuprofen exhibits the desired biological activity.

1.3 Enantioselective reactions

Asymmetric synthesis is a major tool for both the synthesis of natural products and enantiopure molecules employed by the pharmaceutical industry. The field of asymmetric synthesis is very diverse and rapidly expanding in both academic and industrial environments. Early syntheses by pioneers like Robert Woodward set the precedent for the asymmetric synthesis of biologically active molecules, while in later years enatioselective synthesis of natural products such as (-)-strychnine by Overman and the prostaglandin synthesis of Noyori and Corey have demonstrated the potential of modern synthetic methodology (Figure 4).[3]

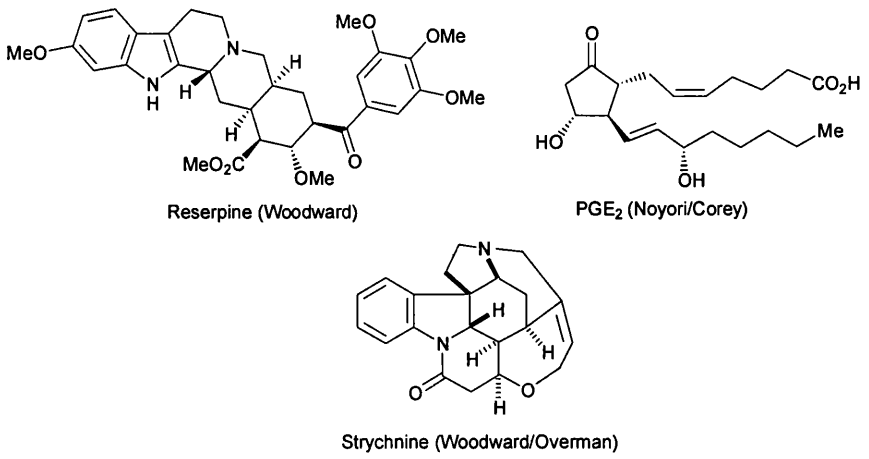


Figure 4: Three compounds synthesised using asymmetric synthetic methodology.

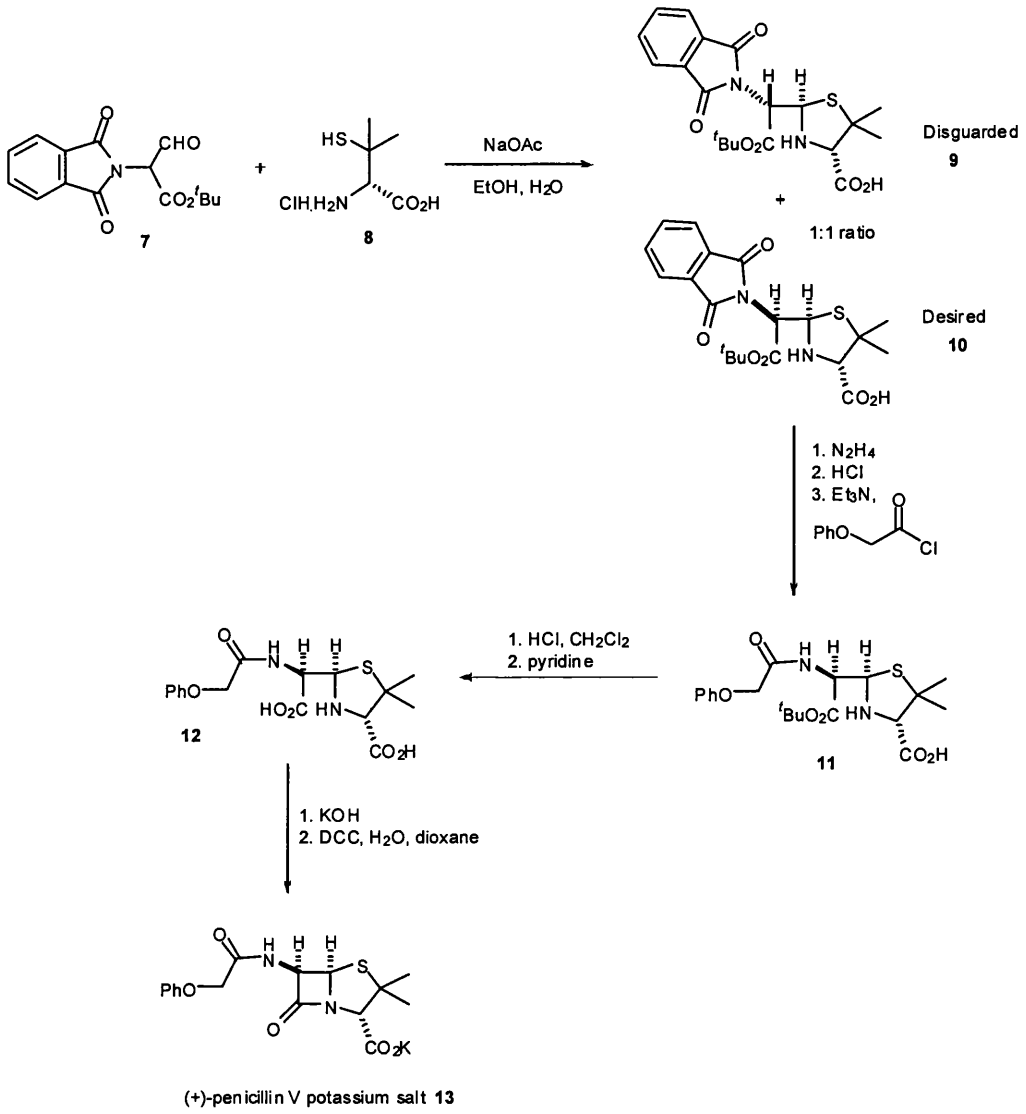
There are various methods employed to achieve an asymmetric synthesis, including the use of:

- Chiral pool approach
- Resolution
- Chiral reagents
- Chiral auxiliaries
- Asymmetric catalysis

The principles of each method, and their relative merits and disadvantages, will now be briefly outlined.

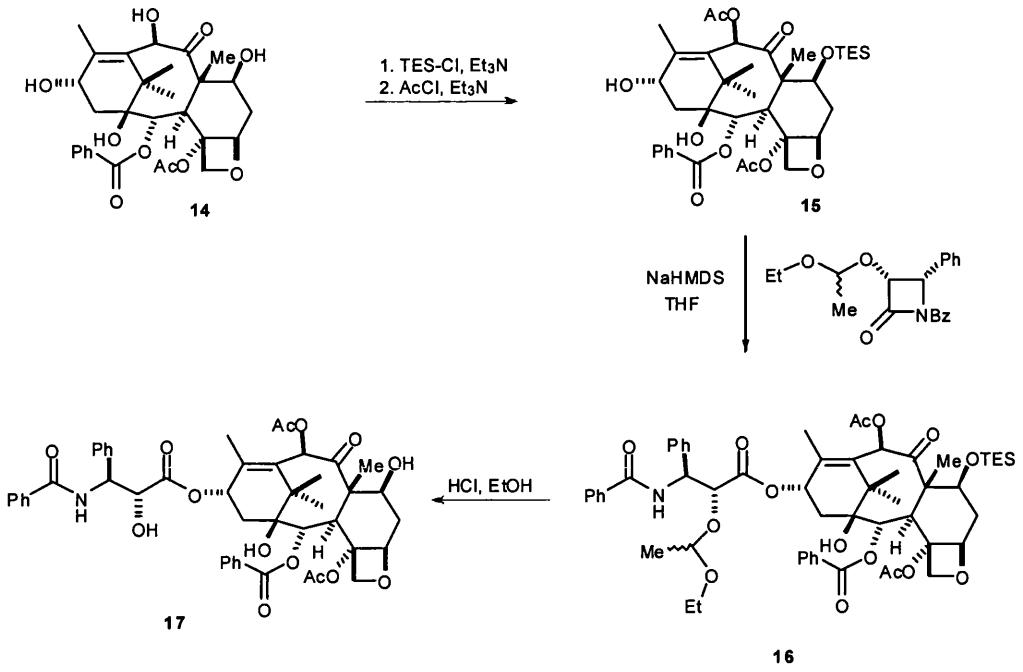
1.3.1 Chiral pool approach

The most economical method for making molecules as a single enantiomer is to synthesise them using an enantiopure natural product starting material. Common examples of naturally occurring enantiopure compounds include amino acids, sugars, steroids, and terpenes. One such example is shown for the synthesis of the β-lactam antibiotic "penicillin V". In this case the hydrochloride salt of naturally occurring D-pencillamine **8** is reacted with phthalimide **7** resulting in a mixture of diastereomeric thiazolidines. These diastereomers were then separated and one of the diastereomers deprotected and reacted with the acyl halide affording the desired amide, which is subsequently lactamised to yield the β-lactam "penicillin V" **13** (Scheme 1).[4]



Scheme 1: Synthesis of penicillin V from chiral pool starting material.

One example where medicinal chemistry takes advantage of the chiral pool is for the synthesis of the anti-cancer drug taxol. Taxol is manufactured today by a semi-synthetic route that uses the naturally occurring 10-deacetylbaccatin III **14**, which can be isolated from the needles of European yew trees. A side chain is attached to the 10-deacetylbaccatin III and Taxol **17** is formed (Scheme 2).[5]

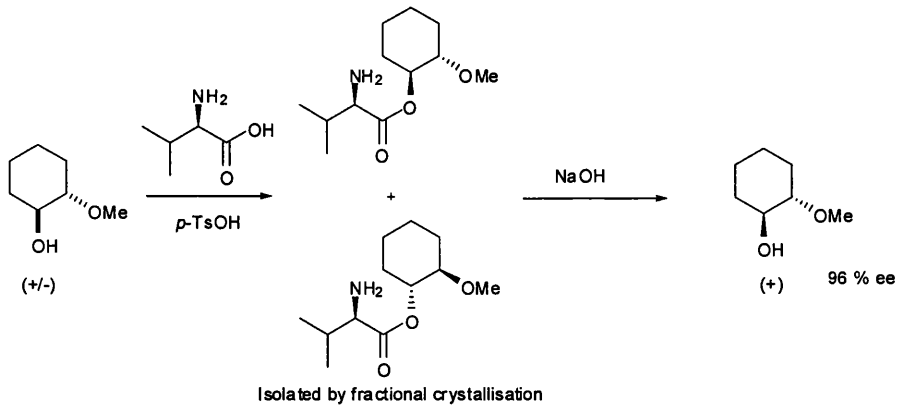


Scheme 2: Synthesis of Taxol from the natural product 10-deacetylbaccatin III **14**.

There are a number of issues associated with the chiral pool approach to asymmetric synthesis. The natural product starting material may only be available in one enantiomeric form. Another problem is that a large number of synthetic steps may be required to remove redundant functionality. Finally, a large quantity of natural product material is often required to produce useful quantities of the target enantiopure compound.

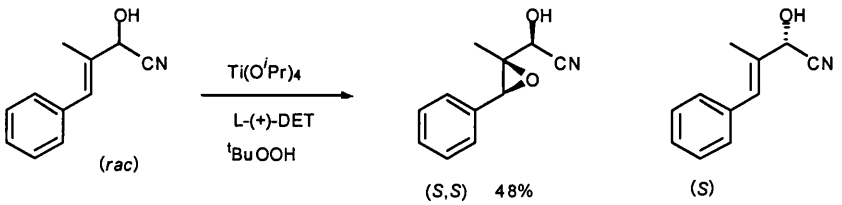
1.3.2 Kinetic Resolution

Classical kinetic resolution using a stoichiometric amount of chiral resolving agent is perhaps the most widely used approach for asymmetric synthesis today. The process involves reaction of a racemic compound with a chiral resolving agent that affords mixtures of diastereomeric products that can be seperated. Such a process can be exemplified by Stead *et al.*, who reacted racemic methoxycyclohexanol with L-Valine, to afford a mixture of diastereoisomeric esters that were separated by fractional crystallisation to afford a single diastereoisomeric ester that was subsequently treated with NaOH to afford enantiopure methoxycyclohexanol (Scheme 3).[6] Unfortunately this process of resolution only allows for a maximum theoretical yield of 50%.



Scheme 3: Kinetic resolution of racemic methoxycyclohexanol.

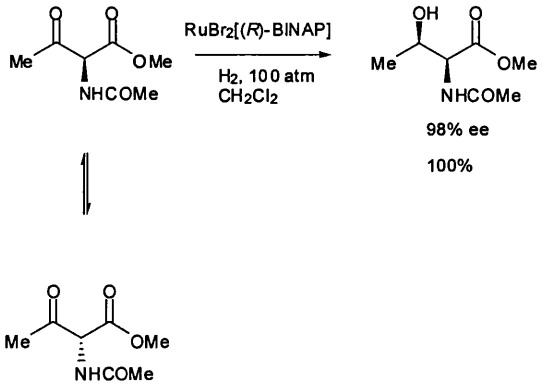
Catalytic kinetic resolution is a method used in asymmetric synthesis whereby a racemic compound is reacted with an enantiomerically catalyst. The chiral catalyst ideally reacts with one enantiomer of the racemic substrate, yielding a new chiral product and enantiomerically pure substrate. For example, Williams *et al.* showed how a racemic allylic cyanohydrin treated under Sharpless epoxidation conditions, afforded a chiral epoxide and the (*S*)-enantiomer of the starting allylic cyanohydrin[7] (Scheme 4). Once again, the problem with this approach is that the maximum yield of the target product is only 50%.



Scheme 4: Kinetic resolution of allylic cyanohydrin using Sharpless asymmetric epoxidation conditions.

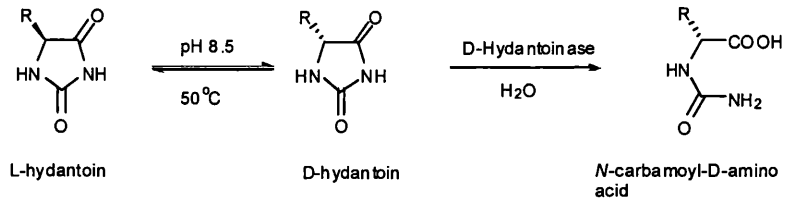
Dynamic kinetic resolution protocols are more efficient than standard kinetic resolution approaches. For a dynamic resolution to occur there must be an equilibrium between the two enantiomers of the starting material. The resolving reagent reacts preferentially with one of the enantiomers, converting it to the desired enantiopure product. However, because the enantiomers of the starting material are in equilibrium, this results in all of the substrate being converted to enantiopure product, to afford yields greater than the theoretical maximum yield of 50% achieved with a standard kinetic resolution.

A common example of dynamic kinetic resolution is the ruthenium-BINAP catalysed hydrogenation of 2-substituted-β-ketoesters. In the reaction shown below the desired chiral β-hydroxyester is formed with a 99/1 *syn/anti* selectivity and in 98% ee (Scheme 5).[8]



Scheme 5: Noyori's catalytic dynamic resolution using a ruthenium-BINAP catalyst.

Enzymes offer a clean and powerful biocatalytic method for carrying out enantioselective resolutions and have often been used for dynamic kinetic resolutions. The example described below demonstrates how a racemic hydantoin can be resolved into enantiopure *N*-carbamoyl-D-amino acid in >50% yield using a hydantoinase catalysed ring opening hydrolysis reaction (Scheme 6).[9]



Scheme 6: Enzymatic dynamic kinetic resolution of racemic hydantoin.

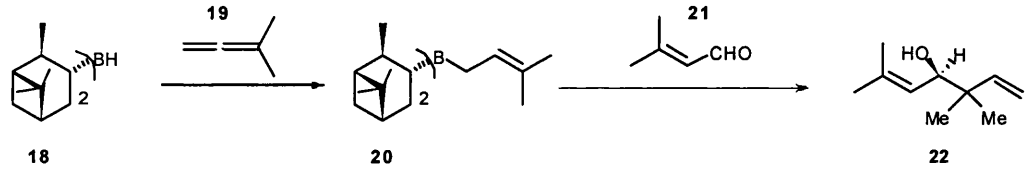
1.3.3 Chiral reagents

Stoichiometric amounts of chiral reagents can react with prochiral substrates to afford enantiopure products with good levels of stereocontrol. An excellent example is the use of a C_2-symmetric dimethylborolane to reduce ketones to their corresponding chiral alcohols with high enantioselectivity. The transition states leading to formation of the

enantiomers are diastereomeric, and as a consequence this reduction reaction can produce enantiomers of the alcohol product in unequal quantities, with the (*R*) enantiomer predominating in high ee (Scheme 7).[10]

Scheme 7: Reduction using a chiral boron reagent.

Another example of the use of a powerful chiral reagent is 3,3-dimethylallyldiisopinocamphenylborane **20** which is obtained by hydroboration of 3-methylbuta-1,2-diene **19** with (-)-Ipc_2BH **18**, that has been used for the asymmetric allylation reaction of aldehyde **21** to afford (+)-artemisia alcohol **22** in 95% ee (Scheme 8).[11]



Scheme 8: Asymmetric allylation of aldehyde **21** using a chiral borane reagent.

1.3.4 Chiral auxiliaries

Chiral auxiliaries are attached to prochiral substrates to control the facial selectivity of an enantioselective reaction. The diagram below depicts how the chiral auxiliary strategy is utilised to achieve an enantioselective transformation. First the chiral auxiliary (**CA**) is attached to the substrate (**S**). This is followed by the required asymmetric transformation resulting in a product possessing a new stereocentre (**P**). The chiral auxiliary is then removed resulting in the desired chiral product and the free chiral auxiliary, which may be recycled for further asymmetric transformations (Figure 5).

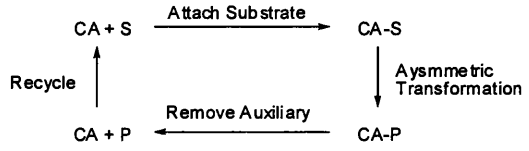
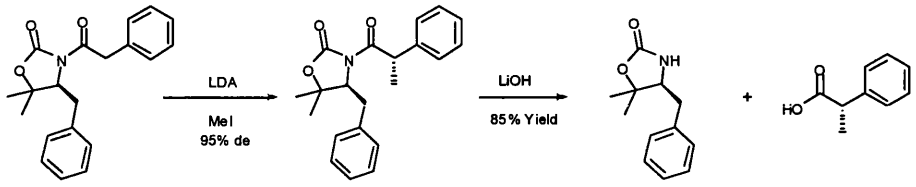


Figure 5: Chiral auxiliaries in asymmetric transformations.

The most well known chiral auxiliaries are those developed by *Evans,*[12] using oxazolidin-2-one auxiliaries that are derived from naturally occurring amino acids which offer good stereocontrol in a range of transformations, whilst being inexpensive and easy to remove (Scheme 9).



Scheme 9: The use of a SuperQuat oxazolidin-2-one to control facial selectivity in an enolate alkylation reaction.

Although chiral auxiliaries often offer excellent levels of stereo control, they are not without their problems. The most notable problem is that stoichiometric quantities of auxiliary are required for the asymmetric transformation. There is also the disadvantage of having to first add the auxiliary and then remove it, with such procedures adding not only extra steps to a synthesis but also the risk of exposing the chiral product to harsh cleavage conditions.

1.3.5 Asymmetric catalysis

The most elegant and economical way to introduce chirality into a molecule is by using a chiral catalyst to promote a chiral transformation.[13] Unlike other methods employed for asymmetric synthesis, catalysis allows sub-stoichiometric amounts of metal-chiral ligand complexes, organocatalysts, or enzymes to be employed in a single step with the catalyst being recovered at the end of the reaction (Figure 6).[14] This compares with chiral auxiliary based transformations which require extra steps for the addition and removal of auxiliary, whilst classical kinetic resolution methods often result in a 50% loss of starting material.

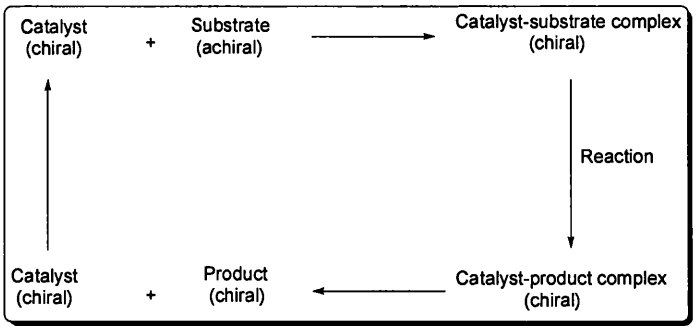


Figure 6: Schematic representation of enantioselective catalysis.

As with all asymmetric syntheses the process of asymmetric catalysis may be explained by the formation of diastereomeric transition states that are different in energy, therefore allowing an enantioenriched product to be formed. This can be exemplified by considering the attack of a Grignard nucleophile on a prochiral ketone. In an achiral reaction, nucleophilic attack occurs in equal amounts at the *Re* and *Si* faces of the carbonyl, forming enantiomeric transition states and as a consequence a racemic alcohol is formed (Figure 7).[14]

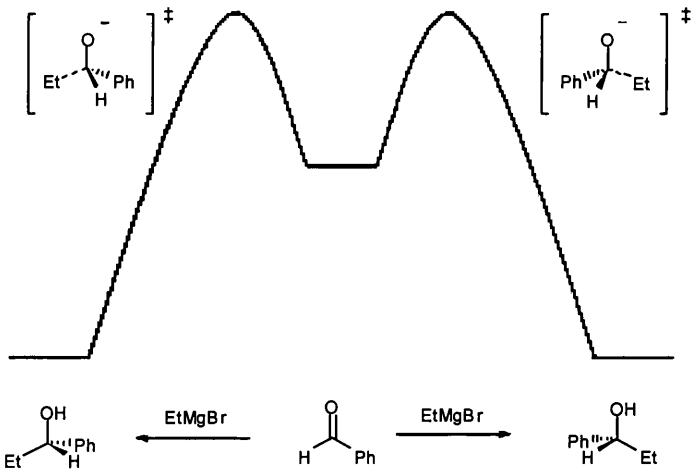


Figure 7: Nucleophilic attack in an achiral environment.

If the same reaction is carried out employing a chiral catalyst, the transition states are now diastereomeric and potentially have different energies relative to each other. It is therefore possible that the reaction may produce enantiomers in different amounts, because the pathway to one enantiomer may be lower in energy and hence kinetically favoured. An example of an asymmetric catalytic reaction of this type is the nucleophilic addition of diethyl zinc to benzaldehyde, in the presence of a catalytic

amount of chiral 1,2-amino alcohol like **24**. This is because the addition of organozinc reagents to aldehydes are relatively slow reactions, except when activated by amines. The use of chiral amine catalysts affords diastereomeric transition states that have a large difference in energy and as a consequence the alcohol product (*S*)-**23** is formed with an enantiomeric excess of 98% (Figure 8).

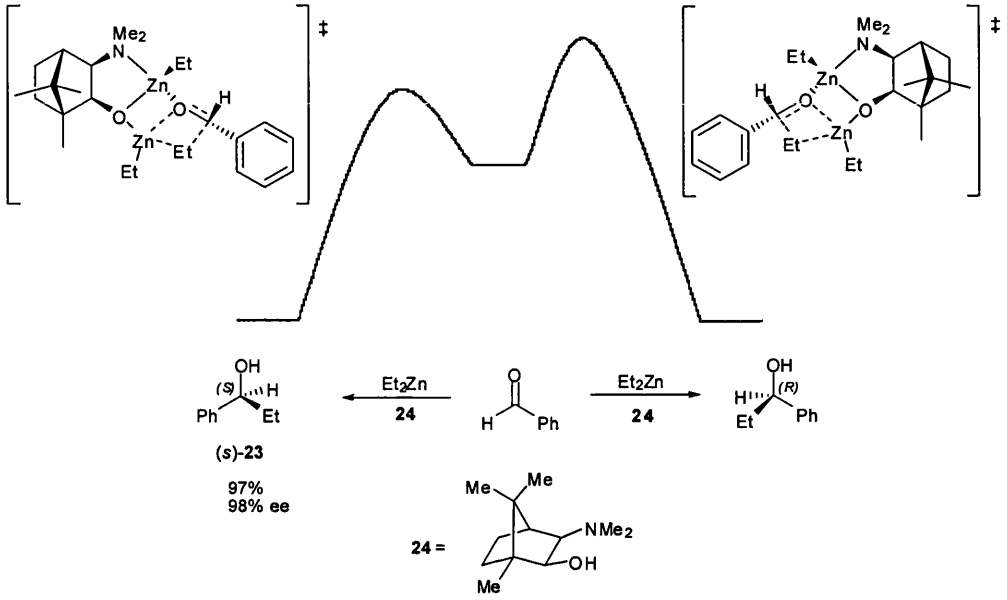
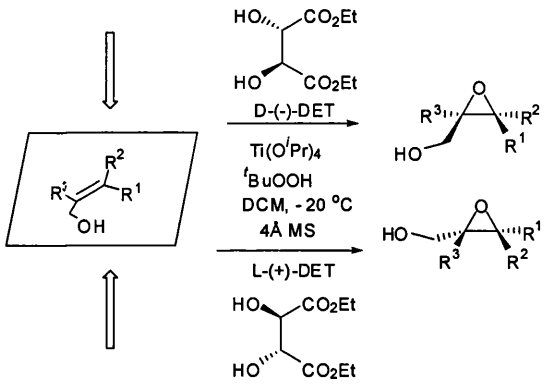


Figure 8: Nucleophilic attack in achiral environment.

The use of organozinc catalysts described above was first discovered by Noyori in 1986. In this example only 2 mol% of amino alcohol **24** was required affording the desired product arising from *Si* face addition of the organozinc reagent.[15]

Perhaps one of the most well known examples of asymmetric catalysis is the Sharpless asymmetric expoxidation of allylic alcohols (SAE).[16] The reaction uses *tert*-butyl hydroperoxide as the oxidising agent, whilst the stereoselectivity is controlled by coordination of a a titanium diethyl tatrate (DET) complex to the hydroxyl group of the allylic alcohol. A catalyst derived from (-)-diethyl tartrate directs epoxidation to the top face (as drawn), while a complex derived from (+)-diethyl tartrate directs' epoxidation to the bottom face of the alkene (Scheme 10).



Scheme 10: Sharpless asymmetric expoxidation of allylic alcohols.

The main disadvantage in using asymmetric catalysts is that they can often prove to be very substrate specific and are normally only useful for one type of reaction. A catalyst that is tolerant to a range of substrates and reaction types would obviously represent an ideal situation.

A wide range of metal-ligand complexes have been developed for organometallic asymmetric catalysis, whose properties can be influenced by the electronic and steric demands of the chiral ligand used for asymmetric induction. In this respect, a large number of chiral Lewis acid catalysts that utilise C_2-symmetrical ligands to achieve good asymmetric induction have been developed (Figure 9), due to the high level of stereocontrol that can be achieved due to their C_2-symmetry properties, that reduces the number of diastereomeric transition states available.[17] The bidentate nature of many C_2-symmetric ligands also decreases the number of coordination sites available to substrates, thus resulting in a higher level of enantioselectivity.

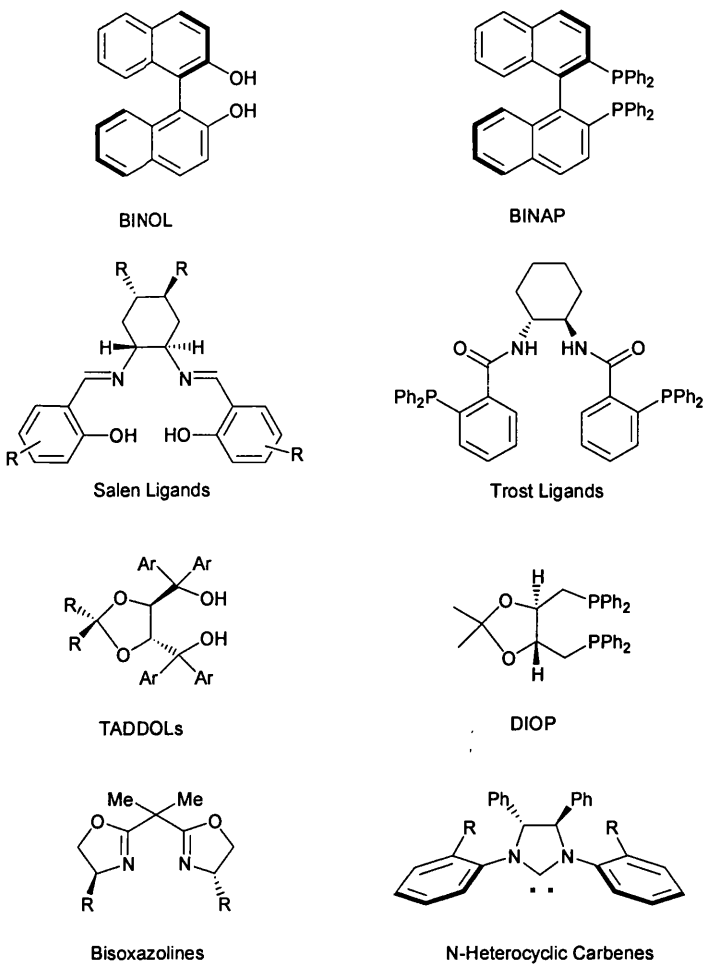
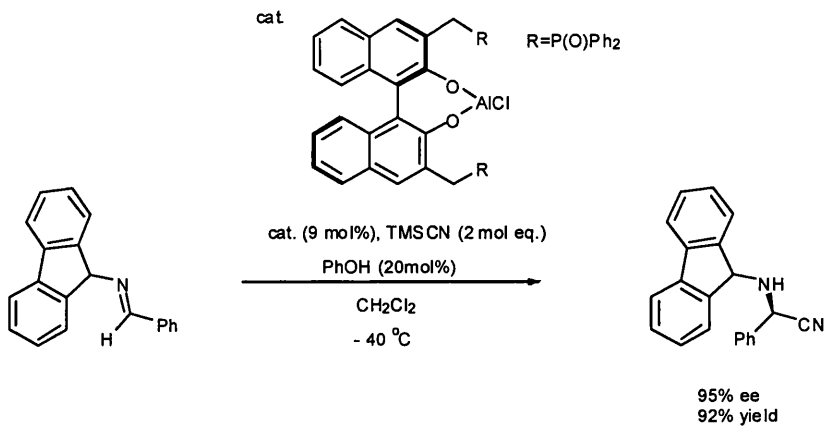


Figure 9: Some commonly employed C_2-symmetric ligands.

For example, these design elements have been employed to develop a C_2-symmetric catalyst for asymmetric Strecker reactions (Scheme 11) where 9 mol% of an enantiopure aluminium-BINOL Lewis acid complex catalyses the asymmetric addition of TMSCN to the imine, resulting in a good yield of (*R*)-aminonitrile with high levels of chiral induction.[18]



Scheme 11: Asymmetric Strecker reaction using a novel C_2-symmetric ligand.

This thesis describes the use of chiral boron-BINOL catalysts for asymmetric aza Diels-Alder reactions, and as a consequence a review now follows describing current methodologies available for carrying out asymmetric aza Diels-Alder reactions of imines with dienes.

1.4 Catalytic Asymmetric Aza Diels-Alder Reactions of Imines

The asymmetric aza Diels-Alder reaction is potentially of great importance in synthesis given the abundance of 6-membered nitrogen containing natural products that have been isolated.[19-21]

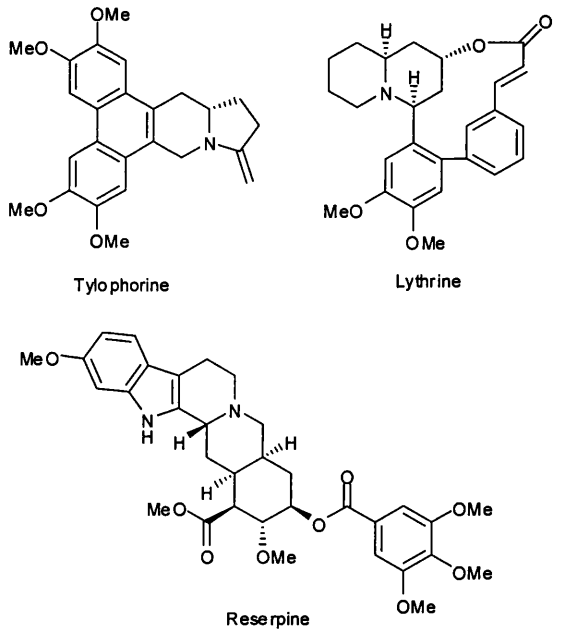


Figure 10: Natural products containing a 6-membered nitrogen ring.

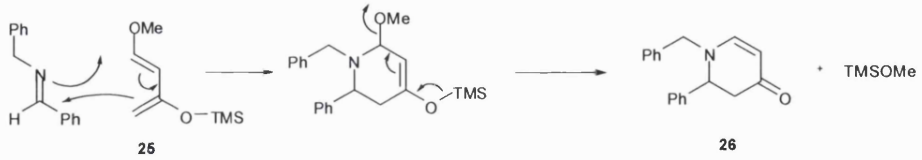
There has been limited progress in the field of asymmetric hetero Diels-Alder reactions of imines has occurred over the last fifteen years or so,[22] primarily due to problems associated with using imines as substrates in catalytic enantioselective reactions. These problems include the Lewis basicity of the nitrogen atom which can result in strong coordination between the imine substrate (or amine product) and the chiral catalyst which can lead to inhibition of catalyst turnover. There is also the problem that imines can exist as mixtures of (*E*)/(*Z*) conformational isomers in solution and the poorer electrophilcity of imine double bond towards incipient nucleophiles. Finally, certain classes of imine contain acidic α protons that can enolize to afford the corresponding enamine.

It should be noted that the following section (**1.5**) contains a review of boron based catalysts that have been used in asymmetric hetero Diels-Alder reactions of imines.[23-26] Consequently, these examples are not discussed in this section, but should be considered within the context of the examples presented in the following section (**1.4**).

1.4.1 Mechanism of the Aza Diels-Alder Reaction

An aza Diels-Alder reaction typically occurs via a formal cycloaddition reaction between an imine (dieneophile) and a diene. In this thesis we are primarily concerned with the aza Diels-Alder reaction between aldimines (imines derived from aldehydes) and Danishefsky's diene **25**, an activated diene first introduced by Samuel Danishesky in the 1970's.[27]

This type of aza Diels-Alder reaction can proceed by one of two mechanisms namely a standard pericyclic [4+2] cycloaddition Diels Alder reaction or a stepwise tandem mechanism based on a Mannich reaction followed by a Michael addition.[28] The first of these reaction pathways follows a concerted Diels-Alder mechanism whereby all bonds are broken and made simultaneously, followed by the subsequent elimination of TMSOMe to afford the target dihydropyridone **26** (Scheme 12).



Scheme 12: The pericyclic [4+2) cycloaddition aza Diels-Alder reaction.

The regiochemistry of the aza Diels-Alder reaction can be explained using the same principles applied to the classical Diels-Alder reaction. Given that the diene is electron rich it is considered that its HOMO reacts with the electron poor dienophile. The regiochemistry of the aza Diels-Alder reaction between the imine and Danishefsky's diene will be dependent on the size of the orbital coefficients,[29] with the largest coefficient of the dienophile HOMO matching with the largest coefficient of the diene LUMO (Figure 11).

Figure 11: Orbital coefficients of the aza Diels-Alder reaction.

The stereochemistry of an aza Diels-Alder reaction is governed by orbital overlap of the diene and dieneophile, which may occur via two different orientations known as *exo* or *endo*. The *endo* transition state is clearly more hindered, however it can often be stabilised due to secondary orbital overlap between the orbitals of the two reactants (Figure 12).

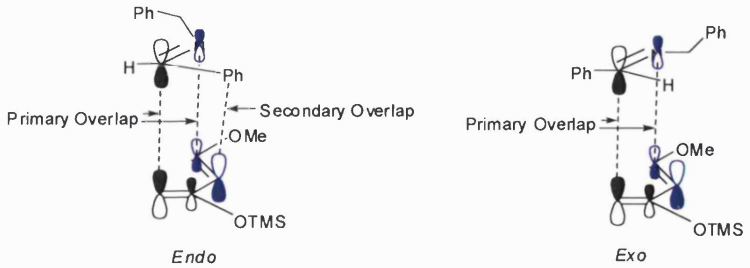


Figure 12: The *endo* and *exo* transition states of the aza Diels-Alder reaction.

The second mechanism follows a stepwise pathway thats proceeds via a Mannich type addition of the silyl enol ether fragment to the electrophilic imine followed by conjugate addition and subsequent elimination of TMSOMe (Figure 13).

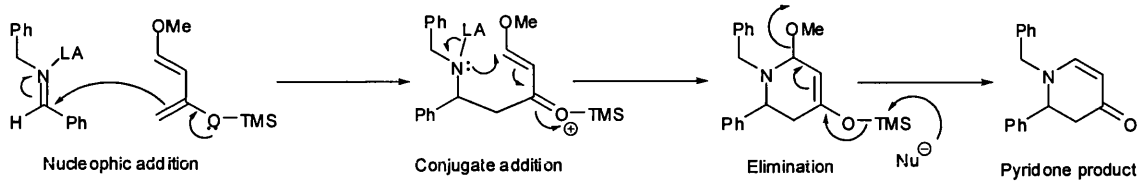


Figure 13: The stepwise aza Diels-Alder mechanism.

The use of a Lewis Acid to catalyse an aza Diels-Alder reaction lowers the energy of the LUMO of the imine thus maximising orbital overlap and facilitating the reaction to occur. Alternatively, for the stepwise reaction, complexation of a Lewis acid to the nitrogen atom of the imine will increase its electrophilicity, thus facilitating nucleophilic attack of Danishefsky's diene (Figure 14). Therefore, the use of a chiral Lewis acid in either reaction scenario potentially allows for control of enantiofacial selectivity in the reaction, thus leading to the formation of enantiopure pyridone product.

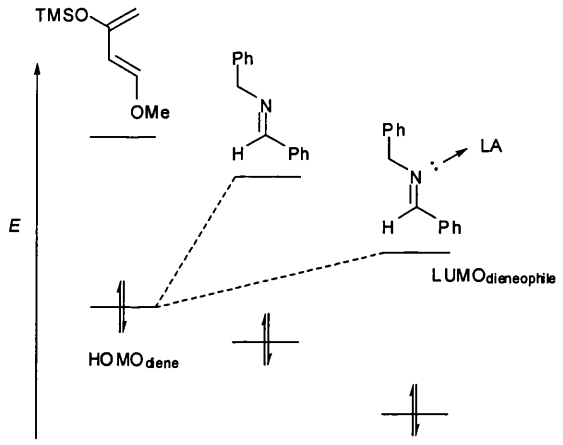
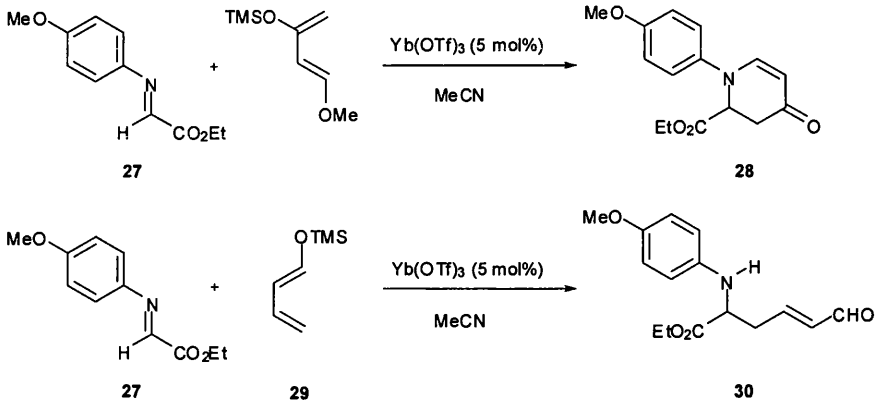


Figure 14: Energy level diagrams showing the effect of a Lewis acid on the HOMO$_{diene}$-LUMO$_{dienophile}$ controlled aza Diels-Alder reaction.

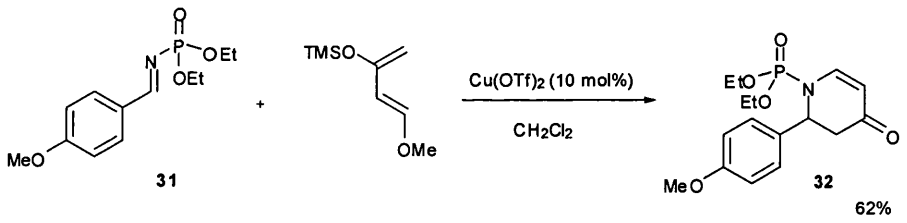
Whiting *et al.* have investigated these reaction pathways in an attempt to further understand which pathways occur under different reaction conditions. They studied

reaction of *para*-methoxyaniline imine **27** with a range of dienes under Lewis acidic conditions.[30] Their first investigation concerned the ytterbium triflate catalysed reaction of imine **27** with Danishefsky's diene, which afforded the desired dihydropyridone **28** in 65% yield. They also treated diene **29** with imine **27** under these conditions which gave aldehyde **30** via a stepwise Mannich-type addition process, with no evidence of any aza Diels-Alder product having been formed (Scheme 13).



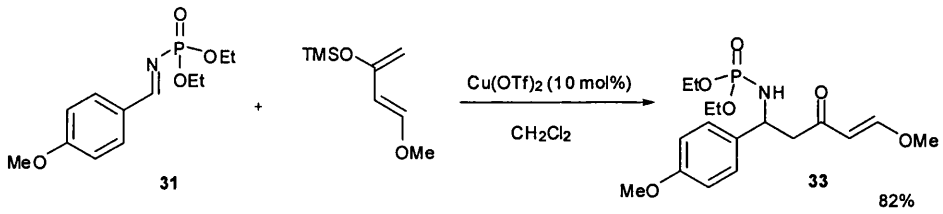
Scheme 13: Lewis acid catalysed stepwise reactions of methoxyaniline imine **27** and various dienes.

Whiting and co-workers continued their investigation into the reaction mechanism by reacting *N*-phosphoryl imine **31** with Danishefsky's diene in the presence of copper (II) triflate (10 mol%) in dichloromethane.[31] The reaction afforded the desired dihydropyridone adduct **32** after acidic work up with TFA (Scheme 14).



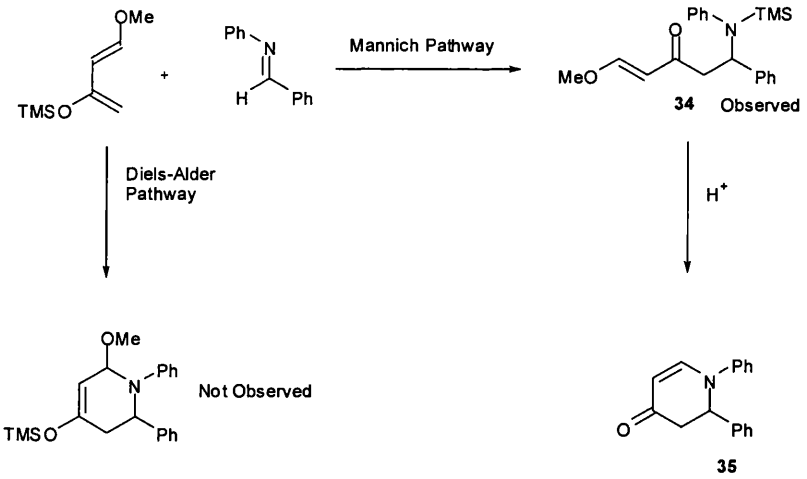
Scheme 14: Reaction of *N*-phosphoryl imine **31** with Danishefsky's diene with an aqueous acidic workup.

The above reaction was repeated under the same reaction conditions, however rather than using an acidic aqueous workup, they worked the reaction up using silica gel, which afforded the Mannich addition adduct **33**, clearly showing that this aza Diels-Alder reaction proceeds via a stepwise reaction mechanism (Scheme 15).



Scheme 15: Reaction of *N*-phosphoryl imine **31** with Danishefsky's diene with silica gel workup.

Ding *et al.* reported that the aza Diels-Alder reaction of Danishefsky's diene with a range of aromatic imines, afforded dihydropyridone adducts in high yields, even when no Lewis acid is employed.[32] The reaction solvent was of great importance to this acid free reaction, with high yields only being obtained in polar solvents such as methanol, acetonitrile, DMF, and with no product being obtained in toluene, CH_2Cl_2 or chloroform. Interestingly ^1H NMR spectroscopy revealed the formation of a Mannich product intermediate **34**, which after acidic work up afforded the desired dihydropyridone product **35** (Scheme 16).



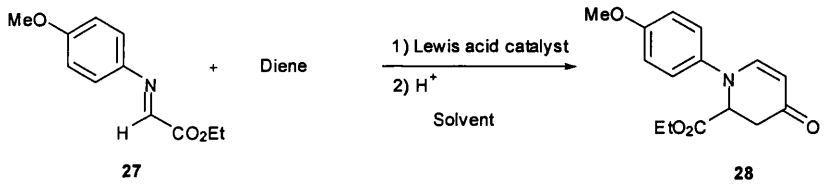
Scheme 16: Formation of Mannich-type intermediate observed.

In conclusion, these investigations clearly show that the Mannich type reaction pathway can occur in both catalysed and non-catalysed aza Diels-Alder reactions using activated dienes, however the formal concerted [4+2] cycloaddition mechanism cannot be completely discounted for certain classes of diene and imine.

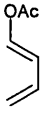
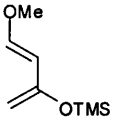
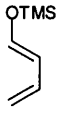
1.4.2 Lewis acid catalysed aza Diels-Alder reactions

A series of investigations have been previously carried out to identify the ideal Lewis acid for the aza Diels-Alder reaction of imines with dienes. Whiting *et al.* have investigated a series of Lewis acids, for the aza Diels-Alder reaction of *N*-aryl imine 27 with a range of dienes in either acetonitrile or toluene.[30] They found that copper (II) triflate or ytterbium (III) triflate were the best Lewis acids for this formation, using either acetonitrile or toluene as solvent (Scheme 17, *a) -- indicates reaction failed*

Table 1).



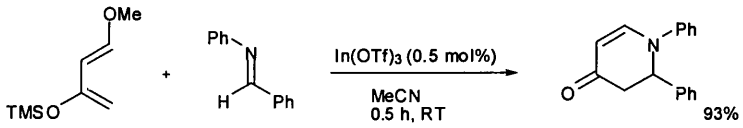
Scheme 17: Lewis acid catalysed aza Diels-Alder reactions using different Lewis acids.

Solvent	*Lewis Acid*				
			OAc	OMe OTMS	OTMS
MeCN[a]	None	--	--	--	--
	$Cu(OTf)_2$	1	2	1	1
	$Yb(OTf)_3$	1	2	1	1
	$Co(acac)_3$	--	--	--	--
Toluene[a]	None	--	--	--	--
	$Cu(OTf)_2$	1	16	1	1
	$Yb(OTf)_3$	1	16	1	1
	$Co(acac)_3$	--	--	--	--

a) -- indicates reaction failed

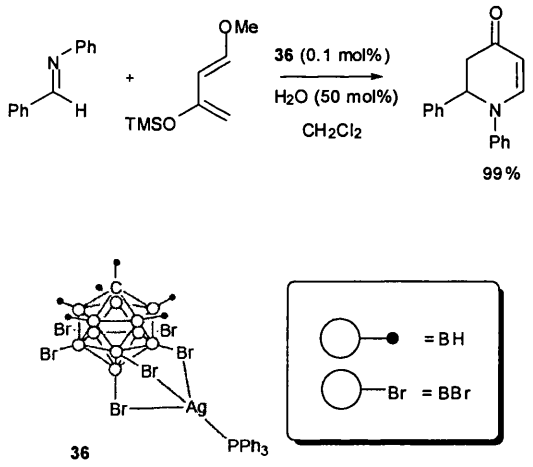
Table 1: Time (hrs) for complete imine consumption in the aza Diels-Alder reaction of various dienes using different Lewis acids in either acetonitrile or toluene. -- Denotes reaction failed.

Frost *et al.* have shown how only 0.5 mol% of indium triflate is required to catalyse the aza Diels-Alder reaction of Danishefsky's diene with *N*-benzylidineaniline.[33] The reaction is remarkably fast, with the target dihydropyridone formed in 0.5 h and in 93% yield. By comparison scandium triflate required 10 mol% loading and a 20 h reaction time to achieve a lower yield of 83% (Scheme 18).



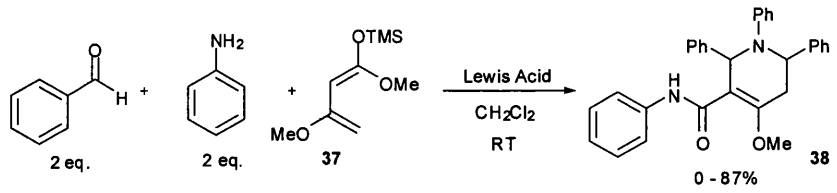
Scheme 18: Indium triflate catalysed aza Diels-Alder reaction.

In addition, Frost *et al.* described how the silver phospane complex utilising a weakly coordinating carborane anion represented an excellent Lewis acid for the aza Diels-Alder reaction of benzylideneaniline and Danishefsky's diene.[34] The product was obtained in quantitative yield after only fifteen minutes using 0.1 mol% of complex **36** (Scheme 19).



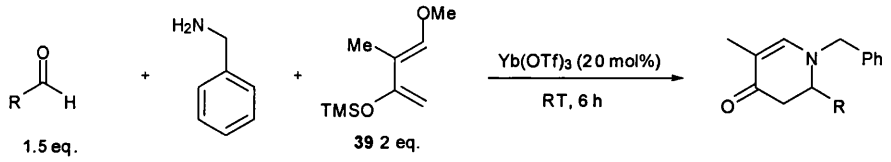
Scheme 19: Aza Diels-Alder reaction catalysed by silver phosphane complex **36**.

Feng *et al.* described their investigation into Lewis acid catalysed aza Diels-Alder reactions carried out under solvent free, microwave conditions.[35] The reaction involved a three component variant reacting aniline and benzaldehyde with Brassard's diene **37**, affording tetrahydropyridine **38**. They found that $BF_3.Et_2O$ gave the highest yield of 87%, although high catalytic loading (50 mol%) was required (Scheme 20).



Scheme 20: Three component coupling for formation of tetrahydropiperidine **38.**

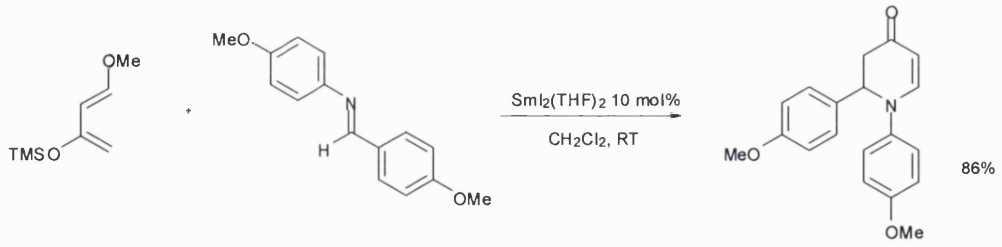
In other research by Feng *et al.* they described how ytterbium triflate is an effective Lewis acid catalyst for the solvent free aza Diels-Alder reaction of benzaldehyde and benzylimine with a modified Danishefsky's diene **39**. They reported that using 20 mol% of ytterbium triflate affords the dihydropyridone adducts in 51 – 86% yield (Table 2).[36]



R	*Mol%*	*Yield, %*
C_6H_5	20	77
4-MeC_6H_4	20	72
3-$MeOC_6H_4$	20	78
2-ClC_6H_4	20	76
2-Pyridyl	20	75
PhCH=CH	20	58
cy-C_6H_{11}	20	86
$(CH_3)_2CH$	20	54
$CH_3CH_2CH_2$	20	51

Table 2: $Yb(OTf)_3$ catalysed three component aza Diels-Alder reaction under solvent free conditions.

Collin *et al.* have also reported how dihydropyridones can be formed in up to 86% yield when the aza Diels-Alder reaction of aromatic imines and Danishefsky's diene is catalysed by 10 mol% samarium diiodide in dichloromethane (Scheme 21).[37]



Scheme 21: Aza Diels-Alder reaction catalysed by samarium diiodide.

Bull *et al.* have developed an air stable C_3-symmetric tris-phenolate titanium Lewis acid **41** formed from complexing titanium tetra-*iso*-propoxide with tris-phenolate **40** (Figure 15).[38]

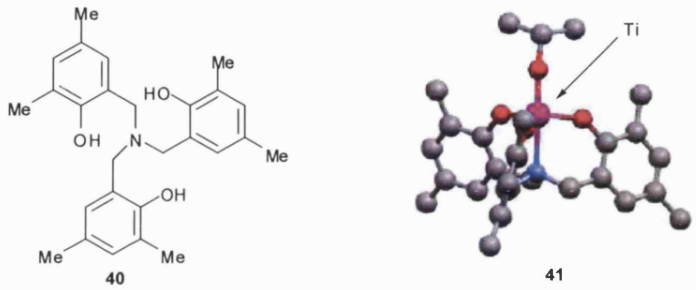
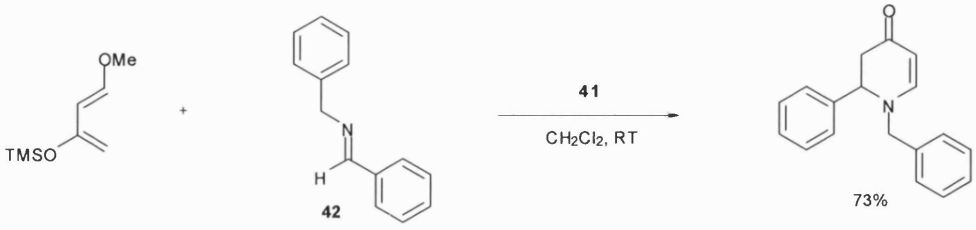


Figure 15: Ligand of the C_3-symmetric tris-phenolate and the crystal structure of the titanium complex.

The C_3-symmetric titanium Lewis acid catalyses the aza Diels-Alder of imine **42** with Danishefsky's diene affording the desired dihydropyridone in 73% yield in less than 10 minutes (Scheme 22).

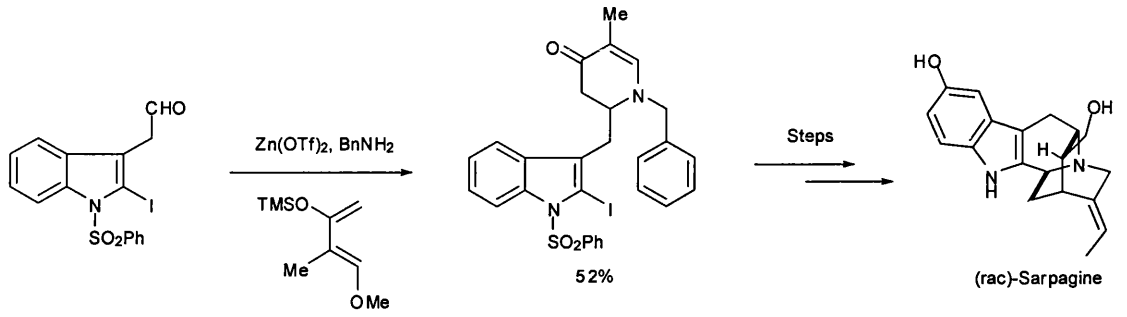


Scheme 22: Aza Diels-Alder reaction catalysed by C_3-symmetric Ti-tris-phenolate complex.

Therefore, it can be seen that the aza Diels-Alder reaction of imines and Danishefsky's diene is a facile process, that often proceeds in a stepwise manner to afford dihydropyridones in good yield. These reactions proceed readily in solvents such as MeOH in the absence of catalyst, whilst a wide range of Lewis acids have been shown to catalyse these aza Diels-Alder reactions in solvents such as CH_2Cl_2 and toluene.

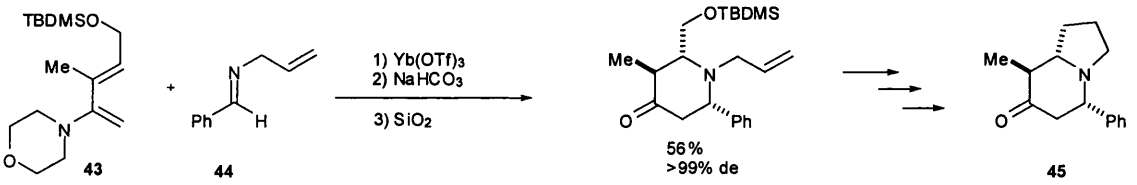
1.4.3 Aza Diels-Alder reaction and natural product synthesis

There have been several reports where aza Diels-Alder reactions have been employed as key construction reactions for the synthesis of natural products. Kuethe *et al.* describe how the aza Diels-Alder reaction of 2-iodo-3-indoleimines, in the presence of zinc triflate, provided 2-(2-iodoindolylmethyl)-4-pyridones in moderate yield, which formed the key framework of ajmaline/sarpagine alkaloids (Scheme 23).[39]



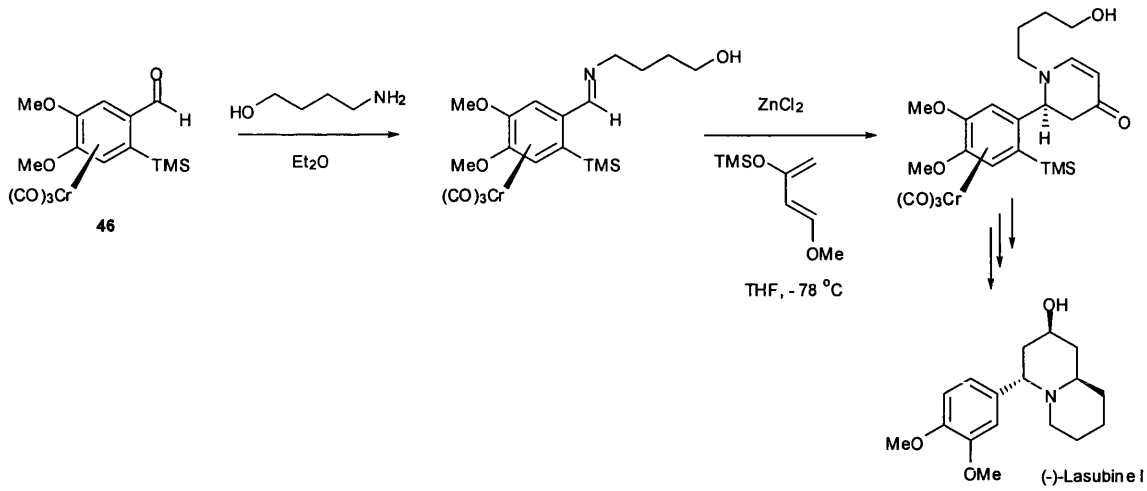
Scheme 23: Aza Diels-Alder reaction of 2-iodo-3-indoleacetaldehyde catalysed by zinc triflate.

Barluenga *et al.* have developed a short and convergent synthesis of 5,8-disubstituted indolizidine scaffolds **45**, with the key step in the synthetic pathway being a ytterbium triflate catalysed aza Diels-Alder reaction of 2-aminodiene **43** with *N*-allylaldimine **44**, followed by ring closing metathesis (Scheme 24).[40]



Scheme 24: Synthesis of indolizidine scaffolds employing an aza Diels-Alder reaction.

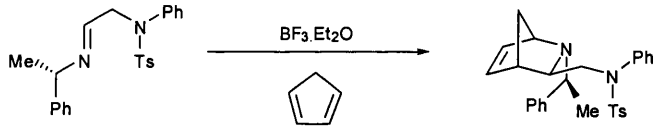
Kundig *et al.* described the synthesis of Lasubine I using an enantiopure planar arylaldehyde tricarbonylchromium complex **46** in a diastereoselective aza Diels-Alder reaction with Danishefsky's diene.[41] The dihydropyridone adduct was then converted to (-)-Lasubine I in four further synthetic steps (Scheme 25).



Scheme 25: Synthesis of Lasubine (I) via an aza Diels-Alder strategy.

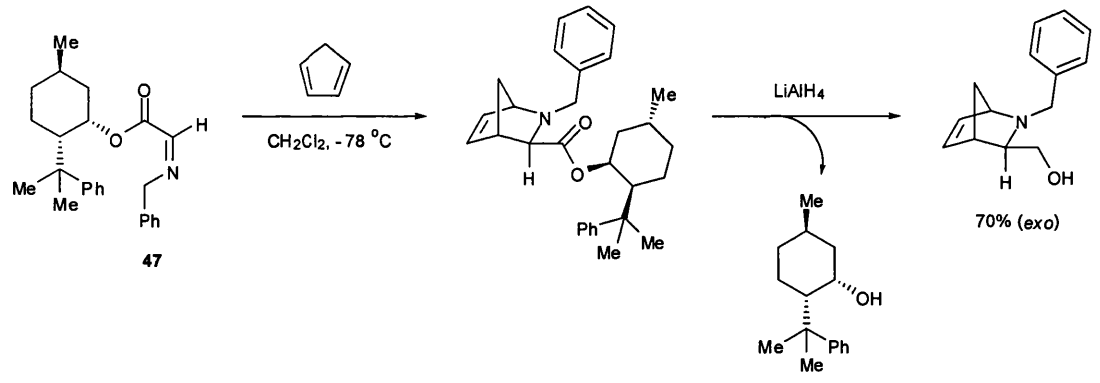
1.4.4 Chiral auxiliary approaches to the aza Diels-Alder reaction

The use of chiral auxiliaries allows for the asymmetric synthesis of aza Diels-Alder adducts, with high levels of enantioselectivity. Andersson *et al.* employed chiral imines derived from enantiopure α-methylbenzylamine for the aza Diels-Alder reaction of enantiopure imines with cyclopentadiene in the presence of $BF_3.Et_2O$ to obtain cycloadducts in a 99:1 diastereoselectivity of the *exo* product with 85:15 *exo* selectivity (Scheme 26).[42]



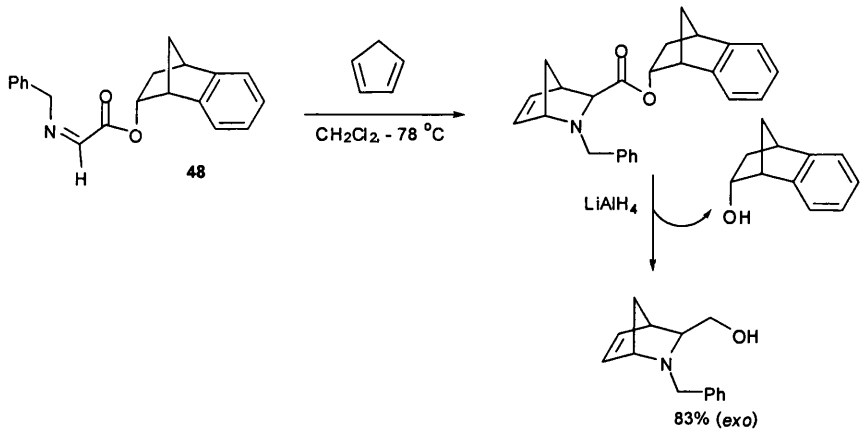
Scheme 26: Aza Diels-Alder reaction using enantiopure imines.

Garcia-Mera *et al.* showed how the aza Diels-Alder reaction of 8-phenylneomenthyl glyoxylate derived *N*-benzylimine **47** and cyclopentadiene resulted in an *exo* adduct as a single diastereomer. The chiral auxiliary controls the facial selectivity of the aza Diels-Alder reaction and was reductively removed via treatment of the cycloadduct with lithium aluminium hydride (Scheme 27).[43]



Scheme 27: 8-Phenylneomenthyl controlled aza Diels-Alder reaction.

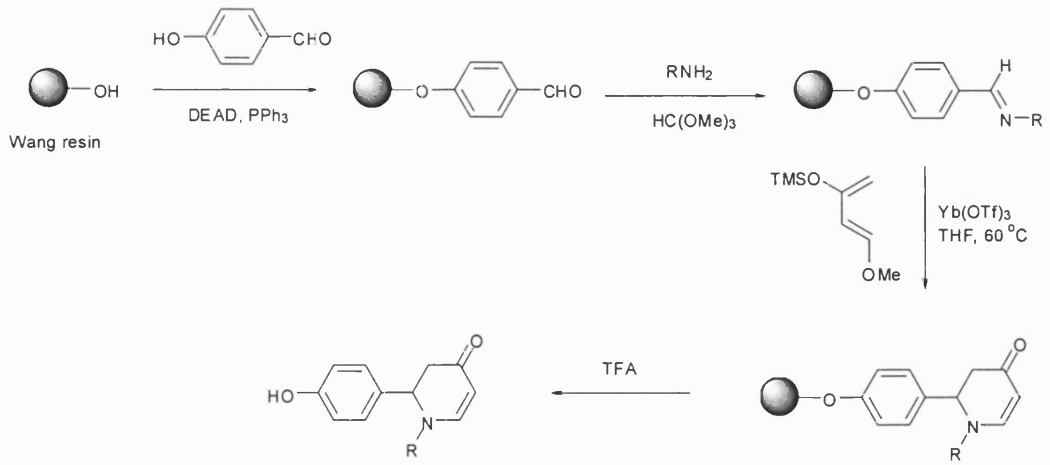
A later paper by Garcia-Mera reported how (+)-(1*R*,*endo*)-2-benzonorbornenol was used as a chiral auxiliary in the asymmetric aza Diels-Alder reaction between cyclopentadiene and the *N*-benzyl imine of glyoxylate **48**, achieving high *exo* selectivity and a diastereomeric ratio of 63:37 (Scheme 28).[44]



Scheme 28: (+)-(1*R*,*endo*)-2-benzonorbornenol as a chiral auxiliary for an aza Diels-Alder reaction.

1.4.5 Solid supported aza Diels-Alder reactions

Wilson *et al.* have reported on the solid supported aza Diels-Alder reaction for the construction of 2,3-dihydro-4-pyridones using ytterbium triflate as a Lewis Acid catalyst.[45] Polymer bound imines were derived from benzaldehydes attached to Wang resin, which were then reacted with Danishefsky's diene in THF at 60 °C. The reaction produced a range of dihydropyridones in yields ranging from 60 – 90% depending on the polymer bound imine substrate used (Scheme 29/Table 3).



Scheme 29: Solid supported aza Diels-Alder reaction.

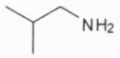
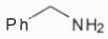
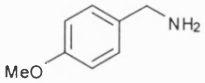
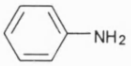
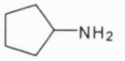
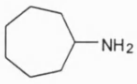
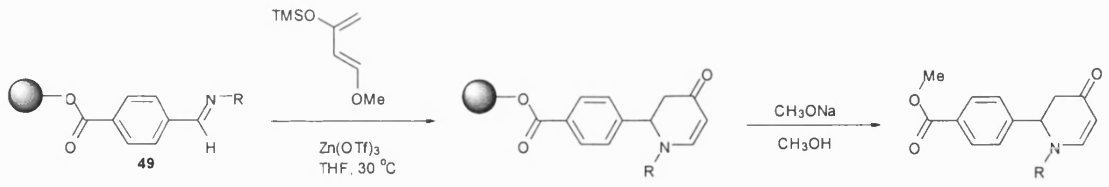
RNH_2	*Yield, %*	*Purity, %*
	90	88
	82	93
	85	90
	80	85
	65	90
	60	70
	75	78
	63	75

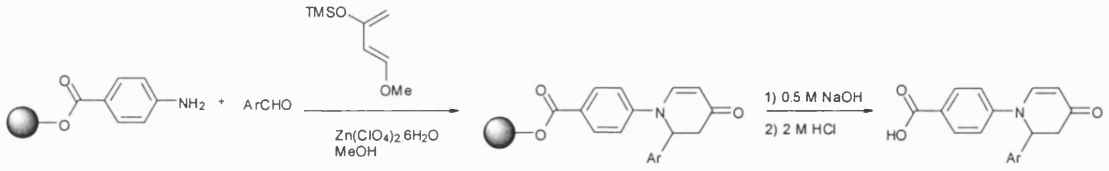
Table 3: Yield and purity data for Wilson's solid supported aza Diels-Alder reaction.

Wang and colleagues utilized PEG bound imines **49** for zinc triflate catalysed aza Diels-Alder reaction with Danishefsky's diene.[46] Following this transformation the polymer bound dihydropyridone was cleaved by sodium methoxide mediated transesterification, in high yields (Scheme 30).



Scheme 30: PEG solid supported aza Diels-Alder reaction.

Alternatively, Ding *et al.* treated a PEG supported amine with a series of arylaldehydes to afford polymer supported imines that underwent aza Diels-Alder reaction with Danishefsky's diene in the presence of zinc perchlorate as a catalyst. Subsequent hydrolytic cleavage under basic conditions afforded dihydropyridone in 48 – 98% yield (Scheme 31).[47]

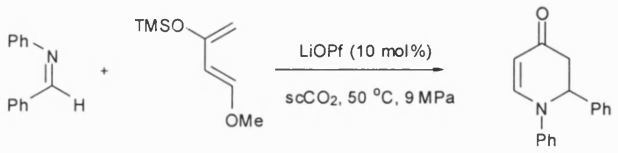


Scheme 31: PEG supported amines for the one pot aza Diels-Alder reaction.

1.4.6 Green aza Diels-Alder reactions

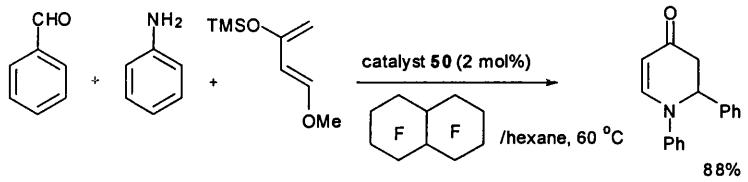
Green chemistry represents a key area of interest within the field of organic synthesis today, with efforts being focussed on the use of environmentally friendly solvents, such as supercritical carbon dioxide, perfluorinated hydrocarbons, ionic liquids or water.

Shi *et al.* used supercritical carbon dioxide as a solvent for the aza Diels-Alder reaction of benzylidineaniline and Danishefsky's diene with a lithium heptadecafluoro-octanesulfonate (LiOPf) catalyst offering an 88% yield of dihydropyridone (Scheme 32).[48]



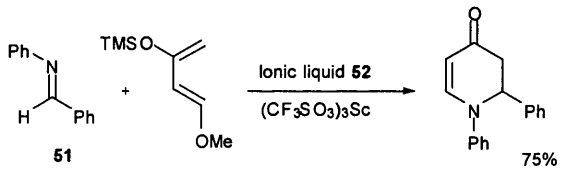
Scheme 32: Aza Diels-Alder reaction carried out in supercritical carbon dioxide

Shi *et al.* also used perfluorodecalin for the fluorous phase aza Diels-Alder reaction using the rare earth metal salt $[Sc(OSO_2C_8F_{17})_3]$ **50** (2 mol%) as a catalyst. This system was successfully employed for the one pot aza Diels-Alder reaction of benzaldehyde, aniline and Danishefsky's diene obtaining an 82% yield (Scheme 33).[49] The use of fluorous phase hydrocarbons is useful given their immiscibility with water, which facilitates reaction workup and product purification.



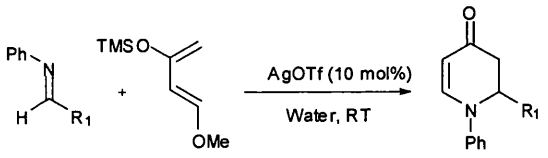
Scheme 33: Aza Diels-Alder reaction carried out in perfluorinated solvent.

Ionic liquids represent a new type of reaction media for organic reactions since their inherent low vapour pressure make them ideal as a recylable solvent for carrying out green chemistry. Examples of aza Diels-Alder reactions carried out in ionic liquids have been reported, including Kitazume who used 8-ethyl-1,8-diazabicyclo[5,4,0]-7-undecenium trifluoromethane sulfonate **52** as an ionic liquid for the scandium triflate catalysed reaction of imine **51** with Danishefsky's diene affording the desired dihydropyridone in 75% yield (Scheme 34).[50]



Scheme 34: Aza Diels-Alder reaction catalysed by scandium triflate carried out in an ionic liquid.

Kobayashi *et al.* described the catalytic aza Diels-Alder reaction of various imines with Danishefsky's diene in water with the best results being obtained using 10 mol% silver triflate as a catalyst which gave dihydropyridones in yields up to 83% (Table 4).[51]



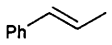
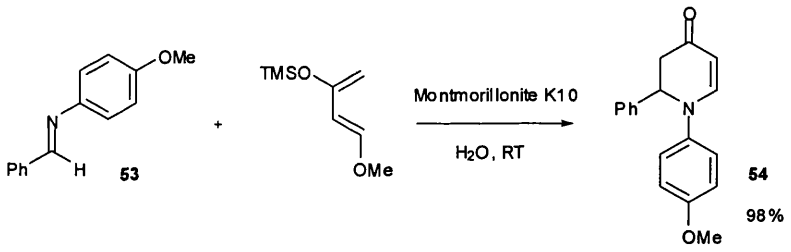
R_1	Yield, %
Ph	83
p-$MeOC_6H_4$	77
p-BrC_6H_4	75
p-$NO_2C_6H_4$	69
	63

Table 4: AgOTf catalysed aza Diels-Alder reaction in aqueous media.

Akiyama and co-workers have reported that the aza Diels-Alder reaction between imine **53** and Danishefsky's diene in water using a solid acid catalyst montmorillonite K10, gave the desired dihydropyridone **54** in 98% yield after a 60 h reaction time (Scheme 35).[52]



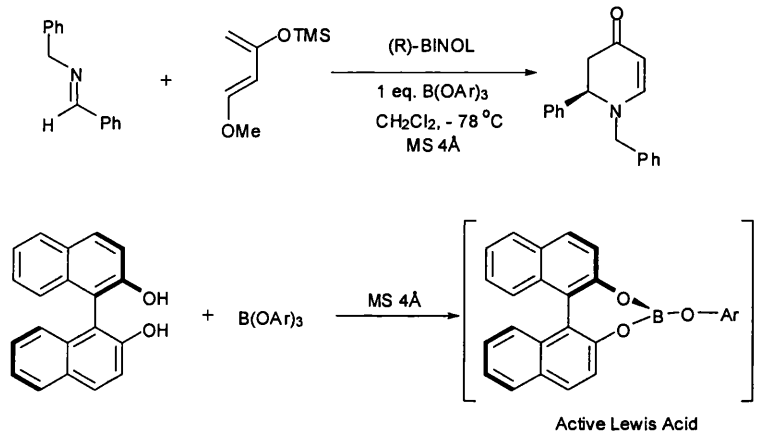
Scheme 35: Montmorillonite K10 catalysed aza Diels-Alder reaction in water.

1.4.7 Asymmetric catalytic aza Diels-Alder reactions employing C_2-symmetric ligands

Given its potential for the synthesis of 6-membered piperidine-like fragments it is unsurprising that much attention has been focussed on developing an asymmetric variant of the aza Diels-Alder reaction. This is a non-trivial undertaking given the propensity of this reaction to proceed in an uncatalysed manner in polar solvents, or in the presence of adventitious acid, to afford racemic products via competing achiral reaction pathways. Nevertheless, there has recently been significant progress in

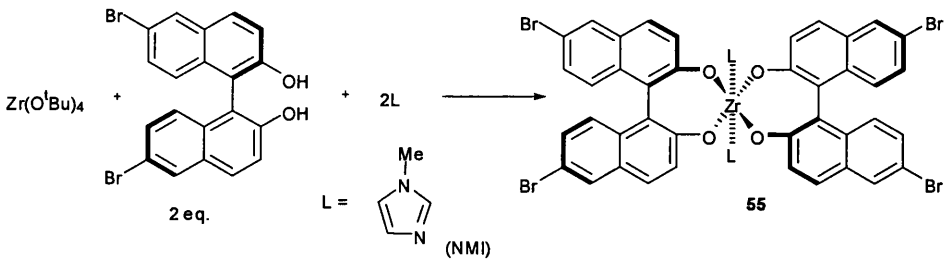
developing asymmetric catalysts for aza Diels-Alder reactions, examples of which will now be reviewed.

As described, C_2-symmetric ligands are commonly used in asymmetric synthesis to afford Lewis acidic metal complexes for catalysts.[53] One of the most common and readily available ligand of this type is binaphthol also known as BINOL. Yamamoto *et al.* successfully developed a boron-BINOL chiral Lewis acid for the aza-Diels-Alder reaction of aldimines and Danishefsky's diene, which required stoichiometric quantities of chiral reagent to achieve high selectivities which will be discussed more fully in the following chapter (Scheme 36).[24]



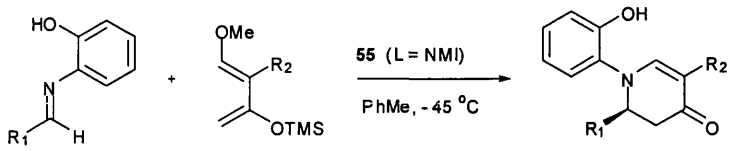
Scheme 36: Boron-BINOL catalysed aza Diels-Alder reaction developed by Yamamoto.

Kobayashi and co-workers managed to improve on this system, by developing the first truly catalytic system in which a chiral zirconium complex **55** was employed for catalysis. This catalyst was prepared *insitu* from mixing $Zr(O^tBu)_4$, (*R*)-6,6'-dibromo-1,1'-binaphthol [(*R*)-Br-BINOL, 2 eq.] and an imidazole or oxazole ligand (Scheme 37).



Scheme 37: Chiral zirconium compound prepared from (*R*)-Br-BINOL and zirconium tetra-*t*-butoxide.

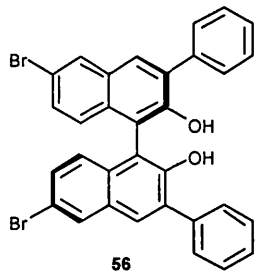
Kobayashi carried out a range of aza Diels-Alder reactions with Danishefsky's diene using reagent **55**[54] with the highest degree of selectivity of 93% ee being obtainied using α-naphthyl-aldimine 20 mol% of reagent **55**, and *N*-methylimidazole (NMI) as a ligand additive (Table 5).



R_1	R_2	*Catalyst, mol %*	*Yield, %*	*ee, %*
α-Nap	H	5	72	67
α-Nap	H	10	86	82
α-Nap	H	20	96	88
α-Nap	H	30	98	89
α-Nap	H	50	88	90
α-Nap	Me	10	79	89
α-Nap	**Me**	**20**	**83**	**93**
σ-MeC_6H_5	H	10	81	76
σ-MeC_6H_5	H	20	83	82
σ-MeC_6H_5	Me	20	97	77
Ph	Me	20	83	65
2-thienyl	H	10	86	64

Table 5: Aza-Diels-Alder reaction catalysed by chiral zirconium reagent **55**.

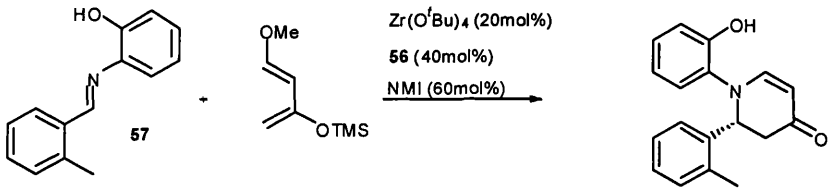
In a later paper published by Kobayashi, it was reported that the enantiofacial selectivity of the aza Diels-Alder reaction could be reversed by modifying the structure of the BINOL ligand employed for catalysis.[55] Therefore, employing (*R*)-6,6'-dibromo-3,3'-diphenyl-1,1'-binaphthol **56** (Figure 16) as a ligand for catalyst formation yielded (*R*)-dihydropyridone in up to 90% ee rather than the (*S*)-dihydropyridone that was obtained previously using 6,6'-dibromo-1,1'-binaphthol as a ligand (Scheme 37).



56

Figure 16: (*R*)-6,6'-dibromo-3,3'-dipheny-1,1'-binaphthol.

The use of **56** in the aza Diels-Alder reaction of aldimine **57** and Danishefsky's diene revealed some other interesting results, including the fact that changing the dimension of the molecular sieves from 5 to 3 angstroms gave a slight increase in enantioselectivity, with the best enantioselectivities being obtained at room temperature in benzene (Table 6).



Solvent	*Temperature, °C*	*MS*	*Yield, %*	*ee, %*
PhMe	- 45	none	66	84
PhMe	0	none	45	57
PhMe	0	MS 3Å	80	90
PhMe	0	MS 4Å	76	89
PhMe	0	MS 5Å	77	89
PhMe	- 45	MS 3Å	54	77
PhMe	23	MS 3Å	96	88
PhH	**23**	**MS 3Å**	**93**	**91**

Table 6: Effect of solvent temperature and molecular sieves.

Building on this success, Kobayashi *et al.* next employed a combination of solid and liquid phase chemistry in an attempt to employ his zirconium-BINOL complexes at lower catalyst loading.[56] The key aspects of the zirconium-BINOL species that were modified (X,Y,Z) in an attempt to gain better reactivity are shown in Figure 17 below.

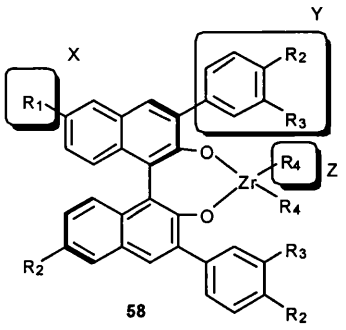
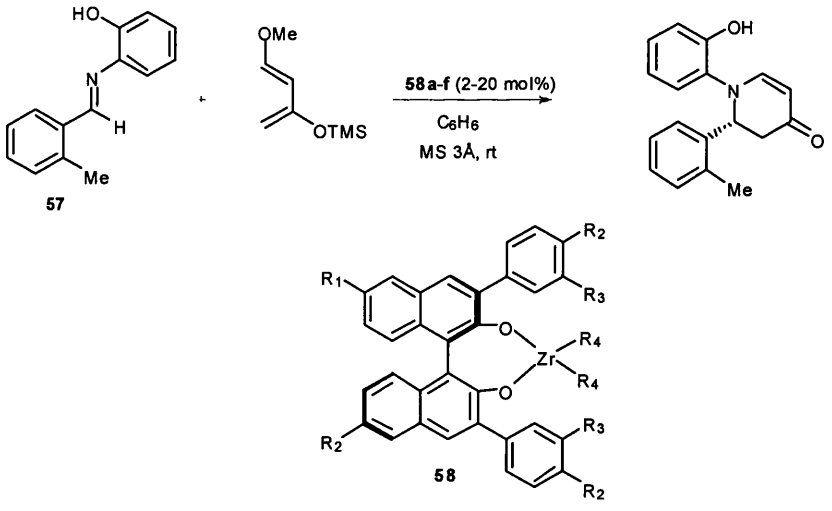


Figure 17: Fragments of the zirconium-BINOL catalyst that were modified.

The first strategy employed was to synthesize solid supported zirconium-BINOL species in a combinatorial fashion which were then used to catalyse the reaction of imine **57** with Danishefsky's diene, in order to determine the best functional groups at the 3 and 3' position of the BINOL ligand. The highest selectivities were achieved when 4-fluorophenyl and 3-trifluoromethylphenyl were present, with the main purpose of the solid support being to ensure that the substituted BINOL ligand could be recovered and reused.

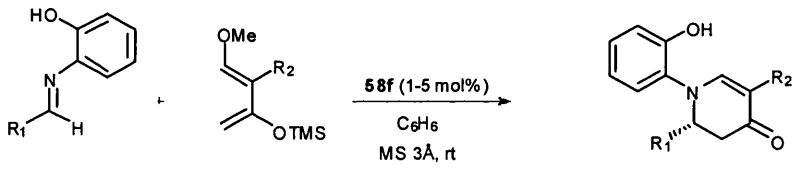
The next stage required the R_1 and R_4 positions of the catalyst to be varied in an attempt to gain the highest ee for the aza Diels-Alder reaction, and it was found that the use of an electron withdrawing cyano group as a ligand for the zirconium metal further increased selectivity at low catalytic loading (Table 7).

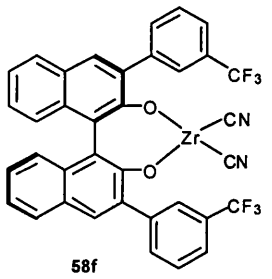


R_1	R_2	R_3	R_4	*Species*	*Mol %*	*Yield, %*	*ee, %*
H	H	H	*t*-BuO	**58a**	20	92	77
Br	H	H	*t*-BuO	**58b**	20	93	91
Br	H	H	*t*-BuO	**58b**	10	82	77
Br	H	H	*t*-BuO	**58b**	5	75	52
Br	H	H	CN	**58c**	20	94	94
Br	H	H	CN	**58c**	10	90	88
Br	H	H	CN	**58c**	5	84	68
Br	H	H	CN	**58c**	2	77	47
H	F	H	CN	**58d**	2	59	73
Br	F	H	CN	**58e**	2	70	77
H	**H**	**CF_3**	**CN**	**58f**	**2**	**73**	**87**
Br	**H**	**CF_3**	**CN**	**58g**	**2**	**74**	**88**

Table 7: Catalyst optimisation using **58** for the reaction of imine **57** with Danishefsky's diene.

The zirconium species **58f** was then selected for the next optimisation stage where the structures of the imine and diene substrates of the aza Diels-Alder reaction were modified to afford dihydropyridone with highest enantioselectivities (Table 8).





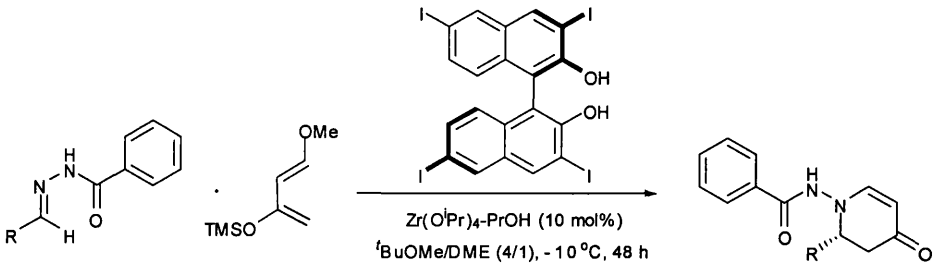
58f

R_1	R_2	*Mol %*	*Yield, %*	*ee, %*
Ph	H	5	76	92
Ph	Me	5	81	91
o-MePh	H	5	93	91
o-MePh	**H**	**2**	**68**	**94**
o-MePh	H	1	64	83
o-MePh	Me	2	72	88
α-Nap	H	5	80	92
α-Nap	H	2	67	86
α-Nap	Me	2	71	84
2-thiophene	H	2	61	83

Table 8: Catalytic asymmetric aza Diels-Alder reaction, using catalyst **58f**.

The best result in these aza Diels-Alder reactions were obtained using an *ortho*-methylphenyl derived imine and Danishefsky's diene with a methyl subsistent at R_2 (94% ee). Kobayashi has further improved on the synthetic utility of this complex **58f** by complexing the zirconium-BINOL catalyst to molecular sieves, to afford an air-stable variant could can be stored open to the atmosphere for extended periods of time which can be completely recovered after the reaction is complete.[57]

Kobayashi also carried out asymmetric aza Diels-Alder reactions of hydrazones again using a chiral zirconium catalyst derived from substituted BINOL ligands.[58] For these reactions zirconium *iso*-propoxide was mixed with 3,3',6,6'-I_4-BINOL which resulted in very high ee's for the reaction of various hydrazones with Danishefsky's diene (Table 9).



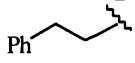
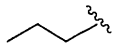
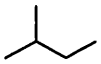
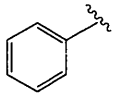
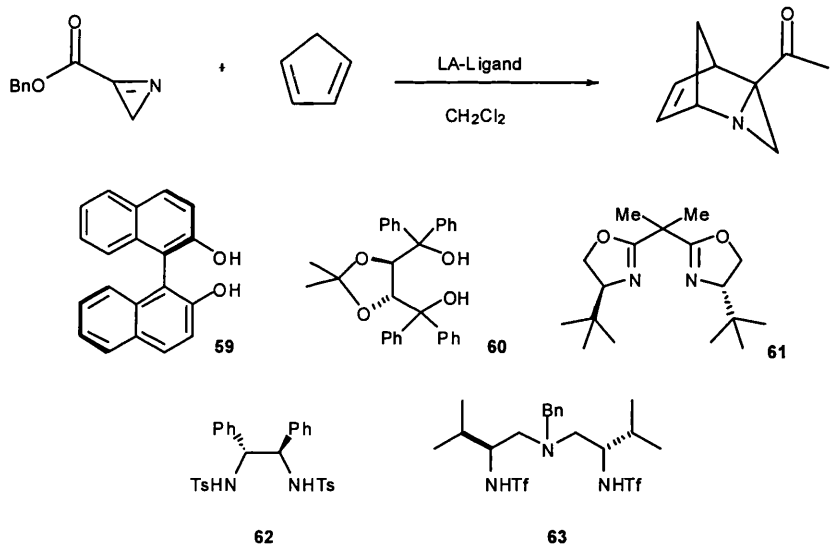
R	*Yield, %*	*ee, %*
	**70**	**91**
	**70**	**93**
	31	92
	44	89

Table 9: Aza Diels-Alder reaction of hydrazones using chiral zirconium catalyst.

Somfai *et al.* described an interesting investigation into the Lewis acid catalysed asymmetric aza Diels-Alder reactions of a *2H*-azirine ester.[59] They used a range of different metal-ligand combinations in an attempt to achieve the maximum possible enantioselectivity for this aza Diels-Alder reaction using cyclopenatadiene to afford *endo*-cycloadducts (Scheme 38).



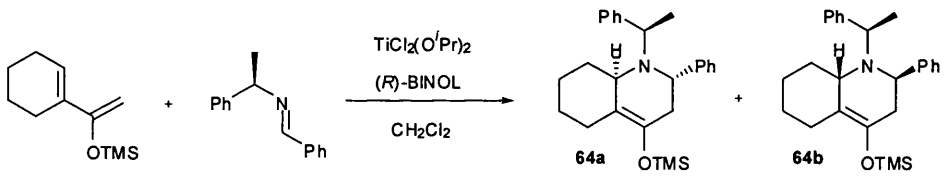
Scheme 38: Aza Diels-Alder reaction of *2H*-Azirines and the various ligands employed for catalyst formation.

The enantioselectivities achieved for these reactions were generally quite low, however to date this is the only example of a Lewis acid catalysed enantioselective reaction using *2H*-azirines as a substrate for an aza Diels-Alder reaction (Table 10).

Lewis acid	*Ligand*	*Temperature, °C*	*ee, %*	*Yield, %*
$AlMe_3$	**59**	**- 35**	**51**	**41**
$AlMe_3$	**60**	- 40	35	27
$Mg(ClO_4)_2$	**61**	- 40	32	22
$Mg(ClO_4)_2$	**61**	- 60	52	25
$AlMe_3$	**62**	- 60	12	22
$AlMe_3$	**63**	- 60	19	20

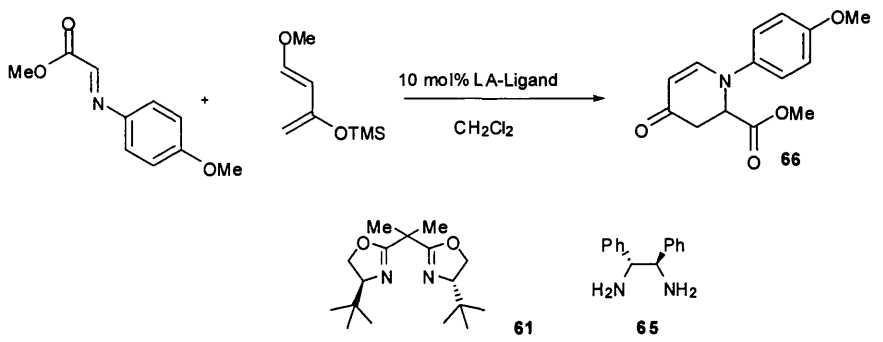
Table 10: Enantioselective Diels-Alder reaction of azirine with cyclopentadiene.

Paugam and colleagues reported the asymmetric synthesis of *N*-phenylethyl-2-phenyldecahydroquinolin-4-ones via a Lewis acid catalysed aza Diels-Alder reaction using a titanium-BINOL complex in sub-stoichiometric quantities (Scheme 39).[60] These reactions involved the addition of a cyclohexene derived dieneophile to an imine containing a chiral auxiliary fragment derived from (*R*)-α-methylbenzylamine, thus affording the opportunity for matched/mis-matched stereocontrol. The levels of selectivity obtained in this reaction were disappointing however, with a diastereomeric ratio of 38:62 being obtained for the formation of **64a**:**64b** in a combined 52% yield.



Scheme 39: Titanium-BINOL Lewis acid catalysed aza Diels-Alder reaction.

Whiting *et al.* initially reported some very high enantioselectivities using bisoxazoline **61** and chiral diamine ligands **65** to catalyse the aza Diels-Alder reaction between Danishefsky's diene and imine **66**, and reported using an extensive combinatorial approach to determine which chiral homogeneous Lewis acid catalysts gave the best enantioselectivities (Scheme 40). The yields reported in these reactions were quoted as moderate however the ee's obtained were generally high with only 10 mol% of Lewis acid being required. Different additives and solvents were reported to be required depending on the type of metal-ligand complex used for catalysis (Table 11).[61]



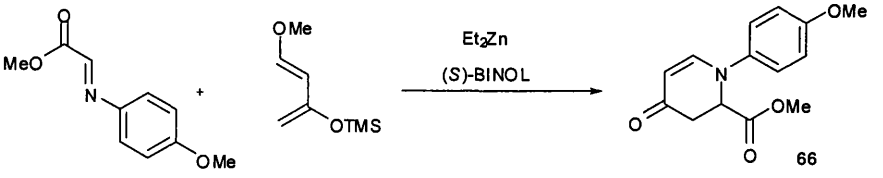
Scheme 40: Aza Diels-Alder reaction of *N*-aryl imines.

Lewis acid	*Ligand*	*Additive*	*Solvent*	*Yield, %*	*ee, %*
MgI_2	**65**	**2,6-lutidine**	**MeCN**	**64**	**97**
$Yb(OTf)_3$	65	2,6-lutidine	PhMe	60	87
$Cu(OTf)_2$	65	none	MeCN	58	86
$FeCl_3$	61	4Å MS	CH_2Cl_2	67	92

Table 11: Reaction of *N*-aryl imine with Danishefsky's diene using chiral ligand-metal complex.

These results were later found to be irreproducible and a *corrigendum* retracting claims of high enantioselectivity in these aza Diels-Alder reactions was subsequently published by Whiting in *Tetrahedron*.[62] The 97% ee quoted for the formation of dihydropyridone **66** using magnesium iodide and the diamine ligand **65** in the presence of 2,6-lutidine, was subsequently reported to be only 55% ee, while all other aza Diels-Alder reactions reported gave no asymmetric induction.

Whiting and co-workers then described an investigation into the asymmetric aza Diels-Alder reaction of a methyl glyoxylate-derived *N*-aryl imine with Danishefsky's diene catalysed by a zinc-BINOL complex. Their initial work focused on finding a suitable metal to be used with enantiopure BINOL ligands. They found that aluminium and boron based systems gave little facial selectivity and quite moderate yields, with diethyl zinc affording an ee of 36% for the formation of pyridone **66**, which acted as the starting point for their investigation (Scheme 41).



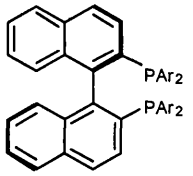
Scheme 41: Aza Diels-Alder reaction of glyoxylate-derived imine with Danishefsky's diene mediated by a Zinc-BINOL complex.

They found that higher selectivities could be achieved when stoichiometric amounts of the zinc-BINOL catalyst were used in methylene chloride, with levels of asymmetric induction and yields of dihydropyridone **66** falling sharply when 10 mol% of catalyst was employed. Other conditions were investigated including changing solvent and temperature and eventually the best conditions were identified using toluene as a solvent at room temperature, using 10 mol% of catalyst that afforded the dihydropyridone **66** in 84% ee but only 52% yield (Table 12).[63] It is interesting to note that lower temperatures resulted in a lower enantioselectivity which is counter intuitive to what might be expected.

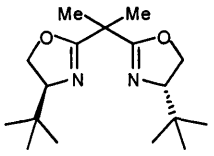
Mol %	*Solvent*	*Temperature, °C*	*Yield, %*	*ee, %*
100	CH_2Cl_2	rt	78	93
10	CH_2Cl_2	rt	62	40
10	THF	rt	61	12
10	MeCN	rt	67	24
10	**PhMe**	**rt**	**52**	**84**
10	PhMe	rt	35	42
10	PhMe	rt	56	17
10	PhMe	0	47	68
10	PhMe	- 40	45	23
10	PhMe	- 78	38	12
10	CH_2Cl_2	0	50	37
10	CH_2Cl_2	- 78	38	7
100	CH_2Cl_2	0	72	92

Table 12: Catalyst loading, temperature and solvent effect of the aza Diels-Alder reaction (Scheme 41).

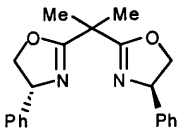
Jorgensen *et al.* investigated the aza Diels-Alder reaction of *N*-tosyl imines derived from ethyl glyoxylate with Danishefsky's diene. They screened a range of transition metals using BINAP and a series of bisoxazoline ligands achieving a wide range of enantioselectivities (Table 13). [64] The best results were obtained using tolyl-substituted BINAP ligands to generate a copper Lewis acid, which gave ee's of 77 - 80%, whereas the use of bisoxazoline ligands afforded only poor to moderate enantioselectivity.



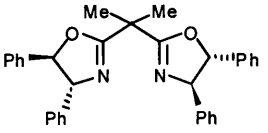
67a: Ar = Ph
67b: Ar = PhMe



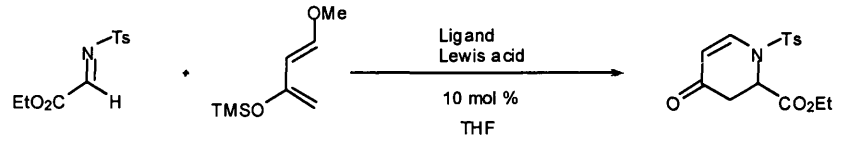
68a



68b



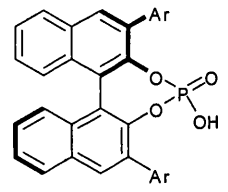
68c



Ligand	*Lewis acid*	*Yield, %*	*ee, %*
67a	$CuClO_4.4MeCN$	65	64
67a	$2CuOTf.C_6H_6$	60	61
67b	**$CuClO_4.4MeCN$**	**68**	**80**
67b	$Cu(OTf)_2$	42	77
68a	$2CuOTf.C_6H_6$	74	12
68a	$Cu(OTf)_2$	60	10
67a	$AgSbF_6$	75	33
67b	AgOTf	85	30
67b	$AgClO_4$	90	34
67b	$Pd(SbF_6)_2$	76	30
67b	$Pd(ClO_4)_2$	68	11
67b	$Pd(OTf)_2$	88	11
67b	$RuSbF_6$	70	0
68b	$Zn(OTf)_2$	74	17
68c	$Zn(OTf)_2$	70	8

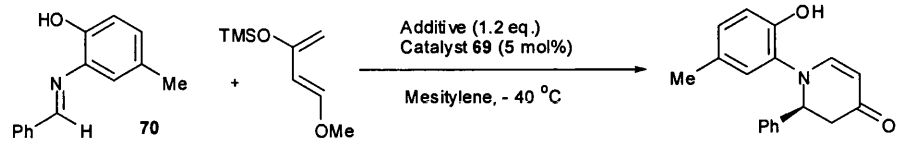
Table 13: Results for aza Diels-Alder reaction with various metal-ligand complexes.

Akiyama and co-workers introduced a chiral Brønsted acid catalyst **69** which they successfully employed for the asymmetric aza Diels-Alder reactions of Danishefsky's diene and aldimines **70**.[65] The chiral acid contained a phosphoric acid fragment derived from BINOL whose enantioselectivity could be modified with various additives with acetic acid proving to be the most successful affording the target dihydropyridone in 67% ee (Table 14).



69

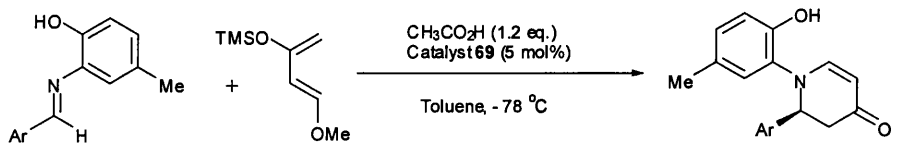
Ar = C_6H_2[2,4,6-(*i*-Pr)$_3$]



Additive	*Yield, %*	*ee, %*
None	29	34
MeOH	97	46
BnOH	81	60
CF_3CH_2OH	88	41
$PhCO_2H$	85	63
CH_3CO_2H	**78**	**67**
$PhSO_3H$	87	15

Table 14: The effect of protic additives on the chiral Lewis acid catalysed aza Diels-Alder reaction.

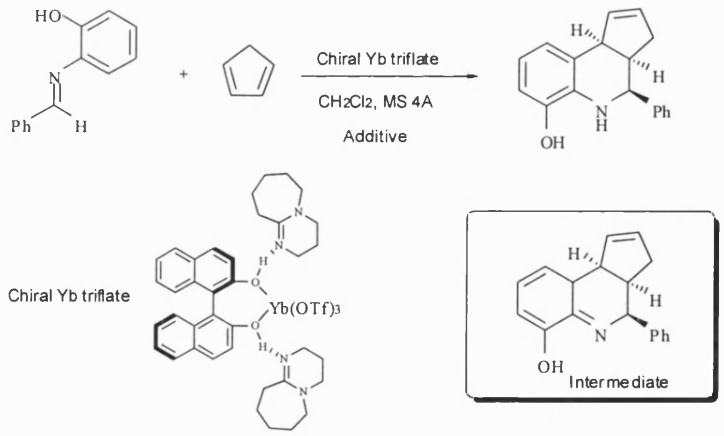
These optimum conditions were then employed for the reaction of Danishefsky's diene with a range of aldimine substrates affording dihydropyridones with enantiomeric excesses ranging from 76 – 91% ee (Table 15).



Ar	*Time, h*	*Yield, %*	*ee, %*
Ph	18	99	80
p-IC_6H_4	24	86	84
p-BrC_6H_4	13	100	84
p-ClC_6H_4	35	72	84
p-FC_6H_4	13	77	78
p-$CF_3C_6H_4$	21	82	81
σ-BrC_6H_4	10	96	80
σ-ClC_6H_4	12	100	76
1-Naphthyl	**12**	**100**	**91**

Table 15: Asymmetric aza Diels-Alder reaction employing chiral Brønsted acid on a range of imine substrates.

Finally, Kobayashi and co-workers have also shown good enantioselectivity for a different type of aza Diels-Alder reaction between *N*-benzylidene-2-hydroxyaniline and cyclopentadiene using a chiral ytterbium-complex Scheme 42)[66] formed from premixing ytterbium triflate with (*R*)-BINOL and DBU. The DBU proved essential to the slectivity of the reaction, since the phenolic hydrogen of the *N*-benzylidene-2-hydroxyaniline was otherwise proposed to interact with the hydroxyl groups of the BINOL ligand, causing a significant drop in selectivity. In this case the reactivity pattern of the aza Diels-Alder reaction is reversed with the imine substrate reacting as the diene fragment and one of the alkene bonds of the cyclopentadiene, acting as the dienophile.



Scheme 42: Catalytic enantioselective aza Diels-Alder reaction using chiral Yb reagent.

A selection of additives were examined with the aim of upping both enantioselectivity and control of the *syn/anti* selectivity at the ring junction, with the best additive being found to be DTBP which was used in stoichiometric quantities in combination with 20mol% of Yb-BINOL Lewis acid (Table 16).

Additive[a] (mol %)	*Temperature, °C*	*Yield, %*	*Syn/Anti*	*ee, %*
none	0	71	98:2	62
none	- 15 – 0	48	99:1	68
NMI (20)	- 15 – 0	21	98:2	91
DTBP (20)	0	49	95:5	31
DTBP (100)	0	67	99:1	61
DMP (100)	0	14	98:2	56
DTBMP (100)	- 15	82	> 99:1	70
DTBP (100)	**- 15**	**92**	**> 99:1**	**71**

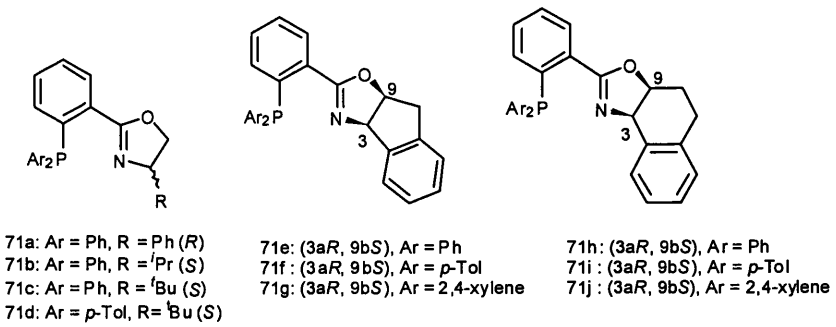
a) NMI: *N*-methyl imidazole. DTBP: 2,6-di-^{t}-butylpyridine. DMP: 2,6-dimethylpyridine. DTBMP: 2,6-di-^{t}-butyl-4-methylpyridine.

Table 16: Effect of additive on the chiral Yb-BINOL catalysed aza Diels-Alder reaction.

1.4.8 Asymmetric catalytic aza-Diels-Alder reactions using unsymmetric chiral ligands

The following section describes a range of aza Diels-Alder reactions that employ chiral ligands that are not based upon a C_2-symmetric scaffold, which also serve to highlight some new developments in chiral ligand design.

Jorgensen and co-workers expanded on their previous work using ethyl glyoxylate-derived imines and Danishefsky's diene by designing a new class of ligand which utilised the features of both oxazoline and phosphine type ligands. Therefore, a new series of chiral phosphino-oxazoline ligands were employed in combination with $CuClO_4$ that proved to be attractive catalysts for the aza Diels-Alder reaction (Figure 18). The yields achieved in these aza Diels-Alder reaction using $CuClO_4$ were particularly high with the best enantioselectivity of 87% ee being achieved when ligand **71c** was used in THF (Table 17).[67]

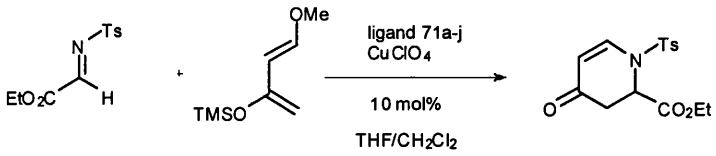


71a: Ar = Ph, R = Ph (*R*)
71b: Ar = Ph, R = ^{i}Pr (*S*)
71c: Ar = Ph, R = ^{t}Bu (*S*)
71d: Ar = *p*-Tol, R= ^{t}Bu (*S*)

71e: (3a*R*, 9b*S*), Ar = Ph
71f : (3a*R*, 9b*S*), Ar = *p*-Tol
71g: (3a*R*, 9b*S*), Ar = 2,4-xylene

71h: (3a*R*, 9b*S*), Ar = Ph
71i : (3a*R*, 9b*S*), Ar = *p*-Tol
71j : (3a*R*, 9b*S*), Ar = 2,4-xylene

Figure 18: Phospino-oxazoline ligands used in copper complexes for aysmmetric aza Diels-Alder reaction.

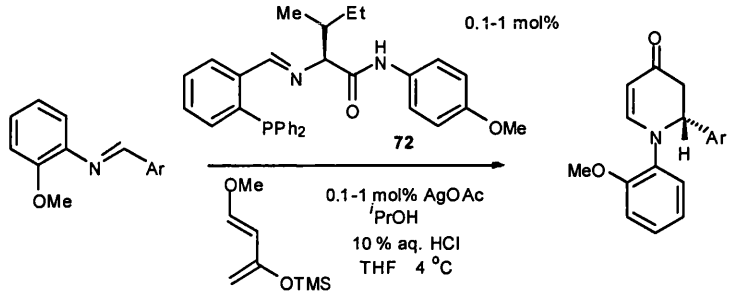


Ligand	*Yield/ee ,%* (*THF*)	*Yield/ee, %* (CH_2Cl_2)
71a	93/27 (*R*)	90/29 (*R*)
71b	97/77 (*S*)	73/71 (*S*)
71c	82/87 (*S*)	96/77 (*S*)
71d	74/87 (*S*)	91/71 (*S*)
71e	94/61 (*R*)	81/62 (*R*)
71f	97/62 (*R*)	93/62 (*R*)
71g	97/79 (*R*)	94/53 (*R*)
71h	49/80 (*R*)	95/75 (*R*)
71i	66/81 (*R*)	77/86 (*R*)
71j	90/66 (*R*)	70/45 (*R*)

Table 17: Aza Diels-Alder reaction of *N*-tosyl α-imino ester with Danishefsky's diene using phosphino-oxazoline ligands.

Hoveyda and co-workers have also developed elegant phosphine ligands prepared from inexpensive amino acid precursors, which when used with silver acetate, affords high enantioselectivities (89-95% ee) for the aza Diels-Alder reaction of OMP-protected aldimines and Danishefsky's diene.[68] The novel Ag-phosphine chiral catalyst was

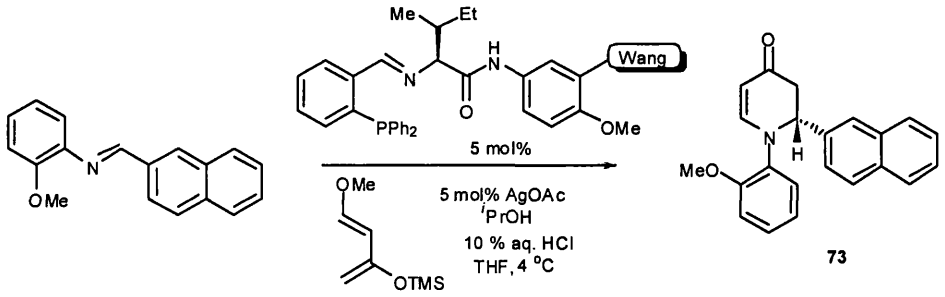
discovered by screening a large number of peptide ligands that were prepared using combinatorial techniques. The phosphine complex described has a high degree of practicality since it can be used in air with undistilled THF, whilst it has also been transferred to solid support to give a fully recyclable catalyst. Some features of this system include the fact that an *σ*-methoxy group is required on the *N*-benzyl fragment of the imine substrate for high levels of enantioselectivity, whilst 1eq. of *iso*-propanol as an additive is required for both good conversion and enantioselectivity (Table 18).



Ar	*72- AgOAc, mol %*	*Yield, %*	*ee, %*
Ph	1.0	94	93
Ph	0.5	92	92
Ph	0.1	78	88
1-naphth	1.0	94	90
2-naphth	0.5	>98	95
p-OMe	1.0	86	91
p-Cl	1.0	98	90
σ-Br	1.0	91	89
m-NO_2	1.0	92	91
p-NO_2	1.0	>98	92
2-furyl	1.0	89	92

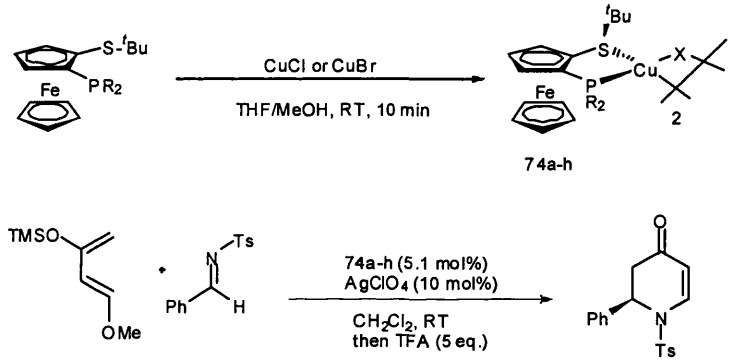
Table 18: Ag-catalysed enantioselective cycloaddition between arylimine and Danishefsky's diene.

Hoveyda also described the asymmetric aza Diels-Alder reaction using the immobilised form of his amino acid based phosphine ligand **72** catalysed an aza Diels-Alder reaction to afford the desired dihydropyridone **73** with an 86% ee and a 96% yield (Scheme 43).



Scheme 43: Solid supported phosphine ligand used in the asymmetric aza Diels-Alder reaction.

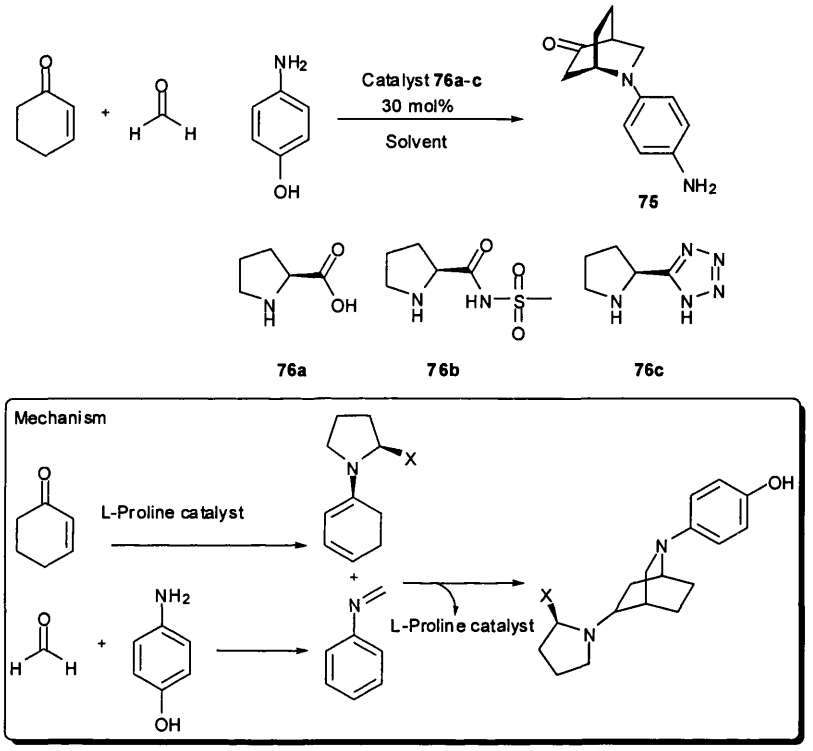
Carretero *et al.* have also described chiral copper complexes of phosphino sulfenyl ferrocenes as efficient catalysts for enantioselective aza Diels-Alder reactions of *N*-sulfonyl imines that afforded a series of dihydropyridones in 55 – 93% ee. (Table 19).[69]



Cu Complex	*X*	*R*	*Time, h*	*Yield, %*	*ee, %*
74a	Cl	Ph	6	79	80
74b	Cl	*p*-FC_6H_4	20	70	71
74c	Cl	2-Furyl	20	58	71
74d	Cl	Cy	20	60	55
74e	Cl	*o*-Tolyl	20	66	57
74f	Cl	1-Naphthyl	3	96	80
74g	Br	Ph	2	89	80
74h	**Br**	**1-Naphthyl**	**1**	**90**	**93**

Table 19: Phosphino sulfenyl ferrocenes as catalysts for the enantioselective aza Diels-Alder reaction.

Finally, Cordova *et al.* described a direct catalytic enantioselective aza Diels-Alder reaction, using L-proline as an organocatalyst to facilitate a three component coupling reaction of 2-cyclohexen-1-one, formaldehyde and *p*-anisidine to afford the desired aza Diels-Alder adduct in up to 99% ee.[70] In this reaction cyclohexen-2-one reacts with the L-proline catalyst **76** to generate a diene intermediate, which then undergoes aza Diels-Alder reaction with an imine species generated *in situ* from condensation of *p*-anisidine and formaldehyde. This represents the first and only method whereby organocatalysis has been employed for an aza Diels-Alder reaction (Table 20).



Catalyst	*Solvent*	*Time, h*	*Temperature, °C*	*Yield, %*	*ee, %*
76a	DMSO	24	RT	30	99
76a	DMSO	*24*	50	52	99
76a	**DMSO**	**24**	**50**	**82**	**99**
76a	DMSO	24	75	45	99
76b	DMSO	24	RT	31	94
76c	DMSO	24	RT	61	99
76a	DMF	24	50	35	98
76a	NMP	24	50	10	97
76a	Toluene	24	50	<5	n.d

Table 20: Amine catalysed direct enantioselective aza Diels-Alder reactions.

1.4.9 Summary

In conclusion it is fair to conclude that only a few successful methodologies for the asymmetric aza Diels-Alder reaction have been developed. Kobayashi has described a zirconium-BINOL system, which affords aza Diels-Alder products with ee's around 80% using only 2 mol% catalyst, however this system is currently limited to a single class of imine substrate. Carretero has shown how copper-phosphino sulfenyl ferrocenes can be employed for the aza Diels-Alder reaction of various imines achieving moderate to high ee with poor to moderate yields, however these ligands can only be obtained after a low yielding multistep synthesis. The same types of problems can be attributed to methodology developed by Jorgensen, whose oxazole-phosphine-copper catalysts afford aza Diels-Alder products with ee's ranging from 27 - 87%, with the requirement that *N*-tosyl glyoxalate derived imines are used as substrates. The best methodology developed so far appears to be the amino acid derived phosphino-silver catalysts created by Hoveyda, where catalytic loading of just 0.1 mol% affords dihydropyridones in nearly quantitative yields and enantioselectivities between 88% and 95% ee.

1.5 Chiral Boron Lewis Acids in Asymmetric Catalysis

There are many examples where chiral boron reagents have been used as chiral Lewis acids for asymmetric transformations over the past thirty years.[71] In this short review of this area a range of boron-ligand complexes that have been employed as Lewis acids in common enantioselective organic reactions will be presented, with particular emphasis being given to Diels-Alder reactions given the subject matter of this thesis.

1.5.1 Boron compounds as Lewis Acids

In this review we look at various chiral boron compounds which act as Lewis acids. The chemistry of boron is such that it usually forms three two-centre two electron bonds resulting in sp^2 hybridisation with angles of 120° between bonds that leave an available empty p orbital available for coordination with nucleophiles. This empty p orbital is responsible for boron acting as a Lewis Acid and it readily forms complexes with Lewis basic compounds to afford neutral tetrahedral species. Alternatively, reaction with nucleophiles result in the formation of "ate" anionic tetrahedral species (Figure 19).[72] Common boron based Lewis acids include BBr_3, BCl_3 and BF_3, and this review will

describe how boron can be complexed to chiral ligands to afford chiral Lewis acids that can act as asymmetric catalyst to deliver stereocontrol.

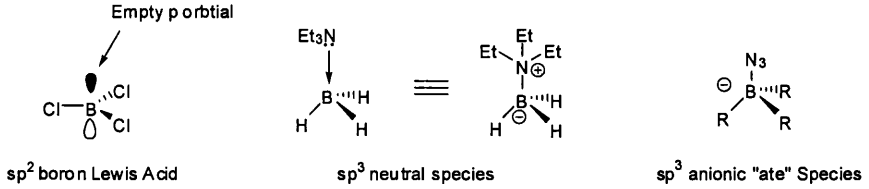
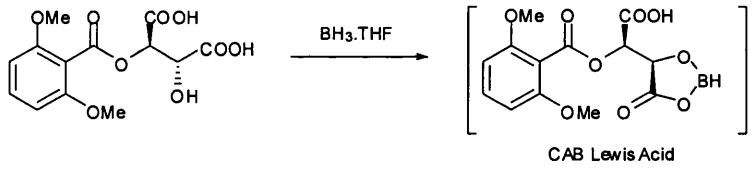


Figure 19: The different species of boron.

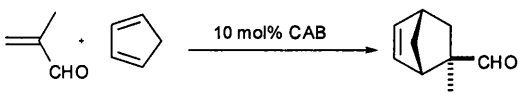
1.5.2 Chiral (Acyloxy)boranes

In the late 1980's Yamamoto and co-workers developed a chiral catalyst prepared from monoacyl tartaric acid and borane, otherwise known as chiral (acyloxy)boranes or CAB catalysts (Scheme 44). They demonstrated how these catalysts could be used for the asymmetric Diels-Alder reaction of a simple achiral α,β-unsaturated aldehyde with various dienes, resulting in good asymmetric induction (Scheme 45).[73,74]



Scheme 44: CAB Lewis acid catalyst derived from tartaric acid and borane.

Yamamoto discovered that an α-substituent on the dienophile increased enantioselectivity, while a β-substituent decreased enantioselectivity significantly, with substituents at both α and β positions resulting in the highest levels of stereocontrol as indicated in Table 21.



Scheme 45: Asymmetric Diels-Alder reaction catalysed by CAB.

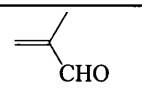
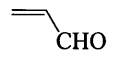
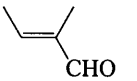
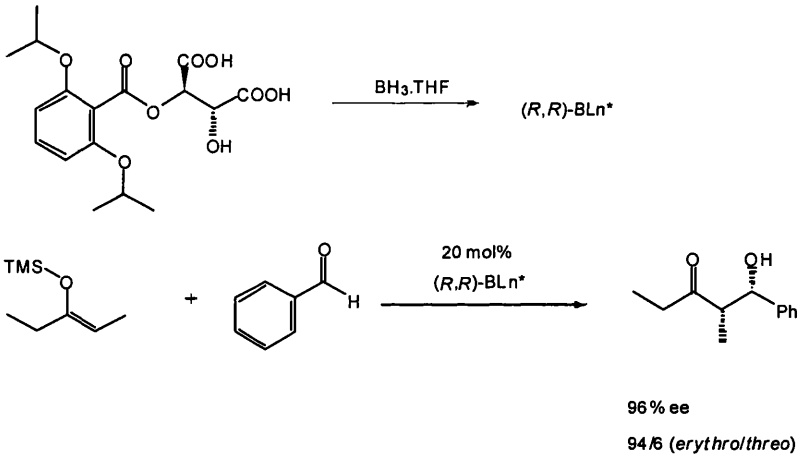
Dienophile	*Diene*	*Temp, °C*	*Time, hours*	*Yield, %*	*Endo/Exo*	*ee, %*
		- 78	6	85	11/89	96 (*exo*)
		- 78	14.5	90	88/12	84 (*endo*)
		- 78	9.5	91	3/97	90 (*exo*)

Table 21: Diels-Alder reaction of cyclopentadiene and α,β-unsaturated aldehyde using 10 Mol% CAB.

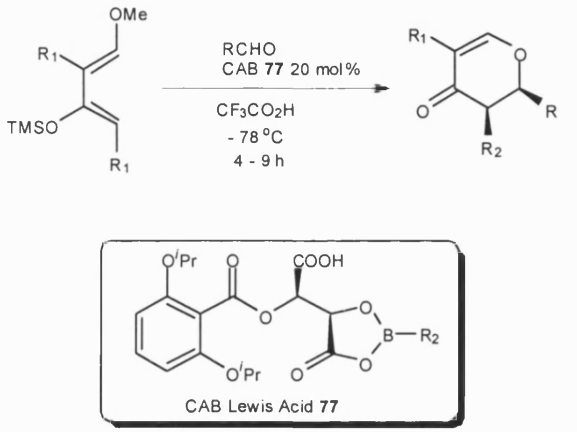
Yamamoto *et al.* also used chiral (acyloxy)borane complex as a chiral Lewis acid for the Mukaiyama aldol condensation of silyl enol ethers and aldehydes.[75] At the time most asymmetric aldol reactions required the use of chiral substrates or auxiliaries in stoichiometric quantities, however this CAB Lewis acid, afforded high enantioselectivities (96% ee) using only 20 mol% of catalyst for efficient conversion (Scheme 46).



Scheme 46: Asymmetric aldol reaction catalysed by chiral (acyloxy)borane (CAB).

Another useful transformation utilising the CAB catalyst is the hetero Diels-Alder reaction, which employs an achiral (acyloxy)borane catalyst in which the boron is now alkylated or arylated. This catalyst **77** is prepared from mixing a tartaric acid derived ligand with an aryl boronic acid which gave excellent results for the hetero Diels-Alder reaction between aldehydes and Danishefsky's diene (Scheme 47).[76] High enantioselectivities were only achieved when R groups were present on the boron of the CAB catalyst which also conferred the advantage of making the catalyst much more stable to air than the previous class of CAB catalyst. The best results were achieved

using a CAB catalyst in which an σ-methoxyphenyl group was attached to the boron atom, giving the desired cycloadduct in 97% ee (Table 22).

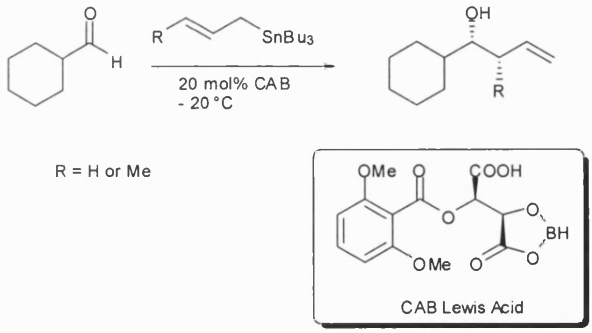


Scheme 47: Hetero Diels-Alder reaction catalysed by CAB catalyst.

Aldehyde	*Diene (R_1)*	*B-alkyl group (R_2)*	*ee, %*	*Yield, %*
PhCHO	H	σ-MeOPh	79	80
		2,4,6-(^{i}Pr)$_3$Ph	95	55
	Me	Ph	87	65
		Bu	93	56
(*E*)-PhCH=CHCHO	H	σ-MeOPh	86	63
	Me	**σ-MeOPh**	**97**	**86**
CH_3CH=CHCHO	Me	σ-MeOPh	92	79

Table 22: Results from CAB catalysed hetero Diels-Alder reaction.

More recently, Marshall *et al.* have demonstrated the versatility of this class of catalyst using a modified CAB Lewis acid prepared from the 2,6-dimethoxybenzoic ester of (*R,R*)-tartaric acid, and 1.5 eq. of a borane THF complex. This complex was used to catalyse the addition of crotyltributyltin or allyltributyltin to a variety of chiral aldehydes, affording *syn* alcohols as major products in 70-90% ee (Scheme 48).[77]

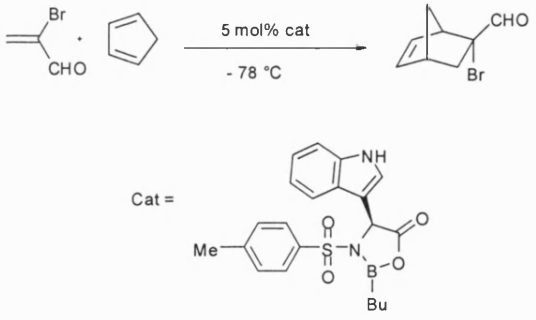


Scheme 48: CAB catalysed addition of organotin reagents to aldehydes.

1.6.3 Chiral Boron Lewis Acids Derived from Amino Acids

A range of chiral boron Lewis acid catalysts have been developed by complexation of borane reagents to enantiopure amino acids. The most well known examples were reported by Corey in the late 1980's where treatment of enantiopure α-amino acids (or their corresponding alcohol) with borane afforded the now famous class of oxazaborolidine catalyst.[78] These CBS catalysts were first employed for the asymmetric reductions of ketones to chiral alcohol, however more recently they have been successfully utilized as chiral Lewis acids in other types of reaction.

For example, Corey *et al.* have employed chiral oxazaborolidines as chiral catalysts for highly enantioselective Diels-Alder reactions, using an *N*-tosyl-(*S*)-tryptophan derived oxazaborolidine to achieve high enantioselectivity (200:1 (*R*/*S*)) and a very respectable 96:4 (*exo*/*endo* CHO) diastereoselectivity, for the reaction of bromacrolein with cyclopentadiene (Scheme 49).[79]



Scheme 49: CBS catalysed Diels-Alder reaction.

This *N*-tosyl-(*S*)-tryptophan derived oxazaborolidine catalyst has been employed widely for the asymmetric synthesis of natural product fragments, including the potent antiulcer substance cassinol **78** and the plant growth regulator gibberellic acid **79** (Figure 20).

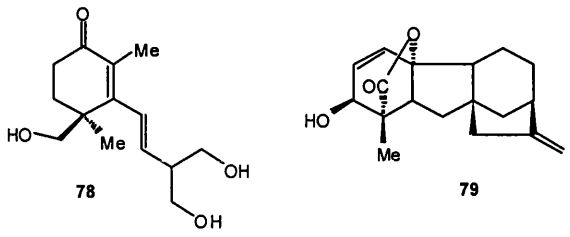
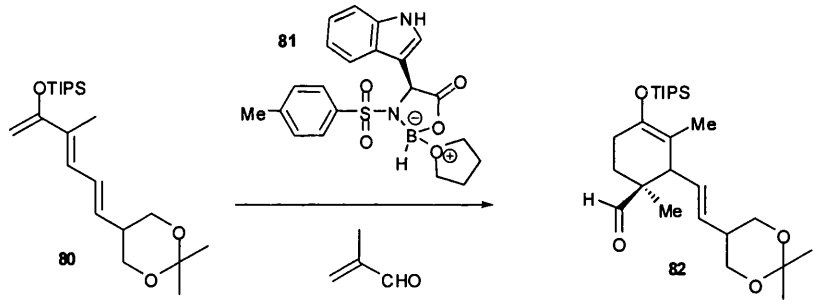


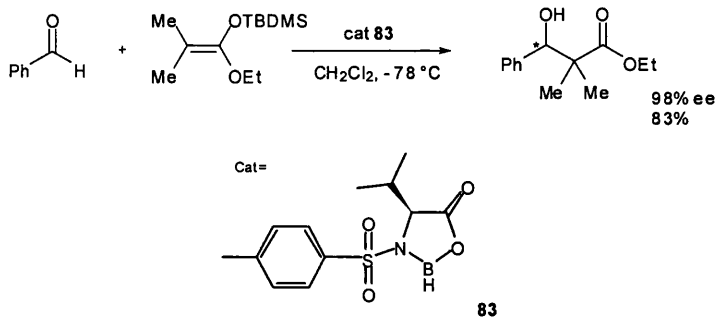
Figure 20: Natural products synthesised using Corey CBS catalysts and the Diels-Alder reaction.

In the case of cassinol, reaction of 2-methacrolein with TIPS-*E,E* triene **80** in the presence of 25 mol% of oxazaborolidine catalyst **81** gave the desired Diels-Alder product **82** with 97% ee, which was a key intermediate for the synthesis of **78** (Scheme 50).[80]



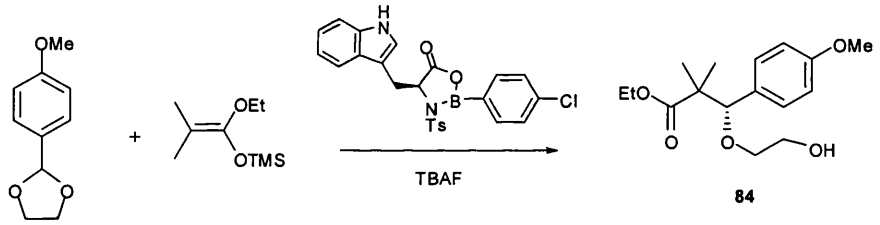
Scheme 50: Synthesis of cassinol key intermediate by CBS catalysed Diels-Alder reaction.

Kiyooka *et al.* have carried out Mukaiyama aldol reactions between silyl ketene acetals and aldehydes using chiral boranes prepared from sulfonamides of amino acids. They observed how these aldol reactions proceeded with high enantiomeric excess's (45-98% ee) when equimolar quantities of chiral boron promoter **83** were used (Scheme 51).[81]



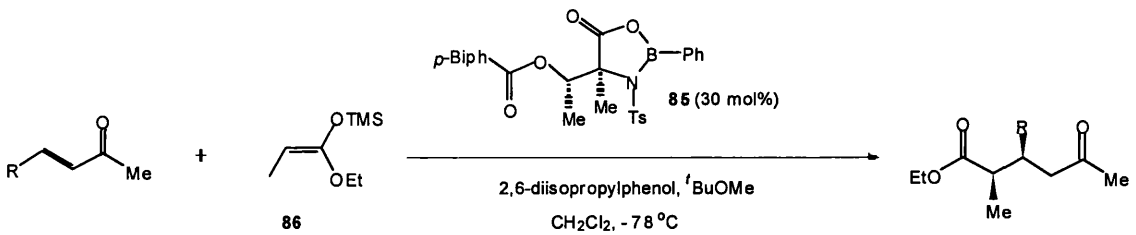
Scheme 51: Borane reagent derived from *N*-sulfonylated amino acid.

Harada and co-workers reported the first example of using an amino acid derived chiral arylboron complex to catalyse the formal aldol reaction of a silyl enol ether with a 1,3-dioxolane substrate (Scheme 52). Complexation of the chiral boron Lewis acid to the dioxolane, affording an oxonium intermediate *in situ* that was then trapped via reaction with silyl ketene acetal, to afford the *O*-protected aldol product **84** in 91% yield and 91% ee.[82]



Scheme 52: Enantioselective ring cleavage reaction using chiral borane reagent.

Harada and colleagues have recently reported on the use of an oxazaborolidine catalyst **85** for the enantioselective conjugate additions of silyl ketene acetal **86** to acyclic enones, affording Michael adducts with enantioselectivities in up to 90% ee and in acceptable yields (Table 23).[83]

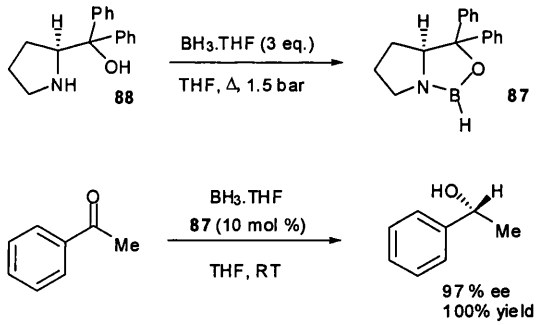


Enone	*Yield, %*	*ee, %*	*Syn/Anti*
R = Ph	**62**	**86**	**16:1**
R = *p*-MeC_6H_4	57	75	8.7:1
R = *p*-ClC_6H_4	53	77	11:1
R = *p*-$CF_3C_6H_4$	**42**	**88**	**>30:1**
R = Me	54	75	8.8:1

Table 23: Enantioselective conjugate additions using catalyst **85**.

1.6.4 Chiral Boron Lewis Acids Derived from Amino Alcohols

The use of amino alcohols as ligands for the development of chiral boron based Lewis acids has been explored vigorously over the past two decades in the Corey laboratories.[78] In the previous section a CBS catalyst derived from the amino acid tryptophan, and its application in asymmetric Diels-Alder reactions was described. These original CBS oxazaborolidines **87** were synthesised by refluxing aminoalcohol **88** with 3 eq. of BH_3·THF in THF and could be used in just 10 mol % loading for the enantioselective reduction of ketones using borane as a stoichiometric reductant (Scheme 53).



Scheme 53: CBS catalysed enantioselective reduction of acetophenone.

The catalytically active species forms via rapid and reversible coordination of BH_3 to the Lewis basic nitrogen atom on the α face of the oxazaborolidine bicycle, affording a

cis oxazaborolidine · BH_3 complex. This coordination of the electrophilic BH_3 to the nitrogen atom activates the BH_3 to become a hydride donor and serves to also increase the Lewis acidity of the boron atom within the five-membered ring, thus allowing coordination of the ketone substrate and hydride transfer to occur (Figure 21).[84]

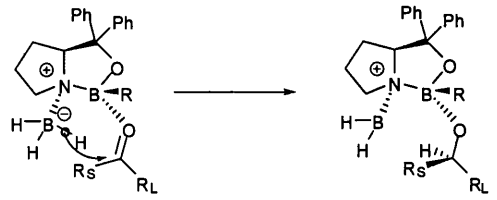
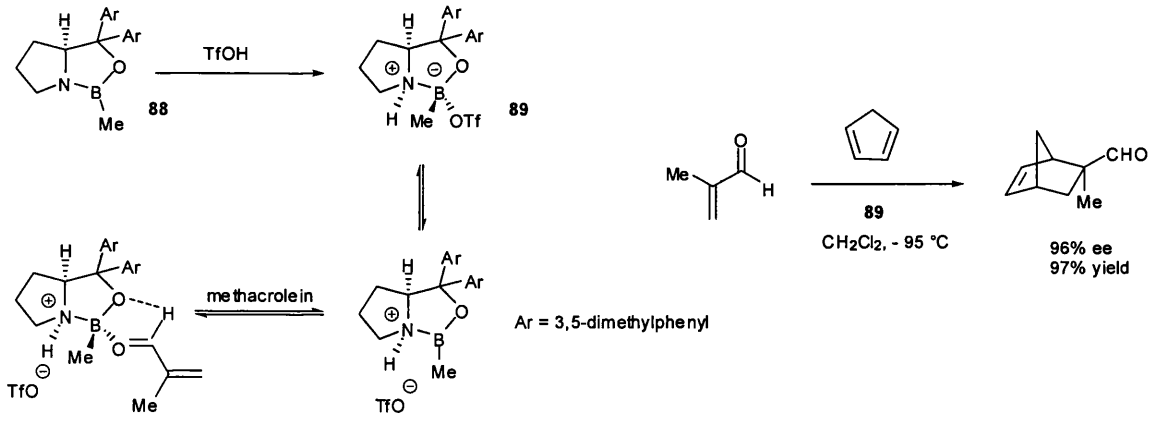


Figure 21: Activated oxazaborolidine for use in enantioselective reductions of ketones.

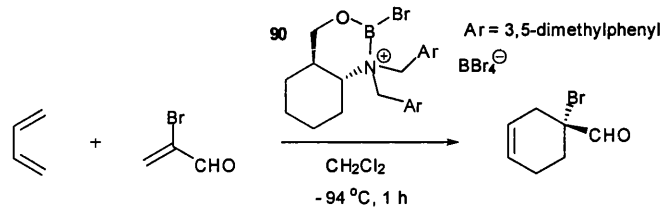
These oxazaborolidines can be converted into potent cationic Lewis acids, via protonation on nitrogen, affording extraordinarily effective catalysts for enantioselective Diels-Alder reactions. For example, when oxazaborolidine **88** is treated with triflic acid a protonated Lewis acid species **89** is formed, which catalyses the reaction of 2-methacrolein and cyclopentadiene forming an *exo*-Diels-Alder adduct in excellent 96% ee (Scheme 54).[85]



Scheme 54: *Exo*-selective Diels-Alder reaction catalysed by oxazaborolidine **89**.

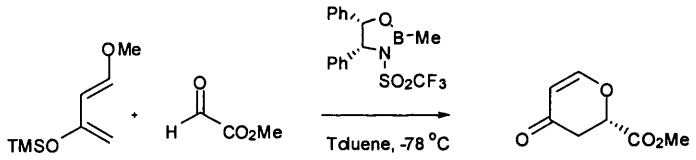
A large number of chiral boron reagents developed to catalyse Diels-Alder reactions were only successful when highly reactive dienes such as cyclopentadiene were used so Corey *et al.* developed novel chiral super-Lewis acids to address this issue. Usually the attachment of bidentate or higher coordination ligands to a Lewis metal centre reduces its acidity due to transfer of electron density from the ligand to the metal. Corey and

co-workers have developed an oxazaborolidine Lewis acid **90**, which is a cationic complex that incorporates a BBr_4^- counter ion, allowing for Lewis acidity levels comparable with BF_3. This boron Lewis acid complex **90** was successfully employed to catalyse reaction between relatively unreactive 1,3-butadiene and 2-bromoacrolein to afford desired cycloadduct in 99% conversion and 94% ee at – 94 °C (Scheme 55).[86]



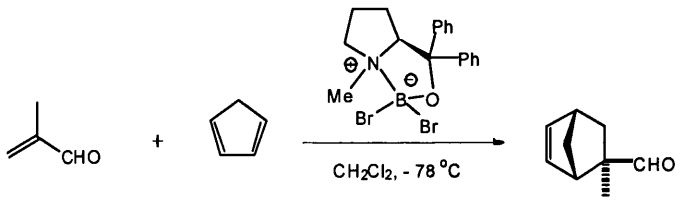
Scheme 55: Diels-Alder reaction of 1,3-butadiene and 2-bromoacrolein.

Mikami and colleagues used a β-amino alcohol derived boron complex as a mild Lewis acid for the asymmetric hetero Diels-Alder reaction between methyl glyoxylate and Danishefsky's diene, affording the desired pyranone in 94% ee (Scheme 56).[87]



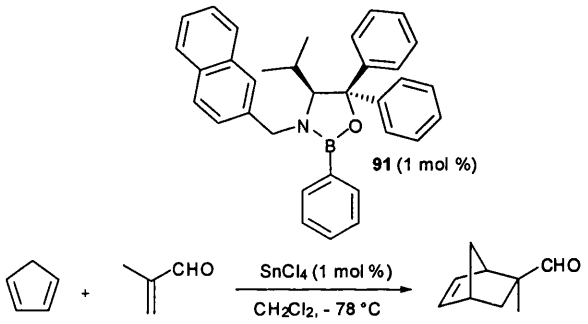
Scheme 56: Reaction of Danishefsky's diene and methyl glyoxylate mediated by chiral boron reagent.

Similary, Aggarwal *et al.* examined a range of amino alcohols as chiral ligands that were complexed to either boron tribromide or boron trichloride *in situ* for the asymmetric Diels-Alder reaction of methacrolein and cyclopentadiene (Scheme 57) and found very high *exo* selectivity.[88] Of all the amino alcohols screened L-*N*-methylprolinol gave the best result, affording the exo-cycloadduct in 97% ee with a de of >99%, whilst other amino alcohols such as cinchonodine and quinidine only gave ee's less than 65%.



Scheme 57: *Exo*-selective Diels-Alder reaction.

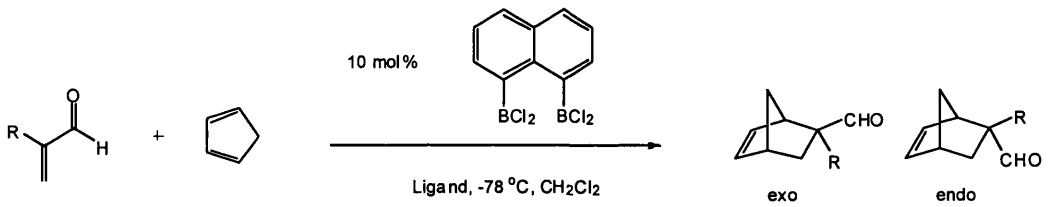
Recently Yamamoto has developed a new type of oxazaborolidine catalyst for highly enantioselective and *exo*-selective Diels-Alder reaction.[89] In previous examples oxazaborolidines were shown to be activated by the addition of Bronsted acids, however Yamamoto adopted a different approach by combining oxazaborolidine **91** with $SnCl_4$ to afford a Lewis acid assisted Lewis acid or LLA. Using this LLA, as a catalyst the reaction of methacrolein and cyclopentadiene gave the *exo*-cycloadduct in 95% ee at -78°C (Scheme 58).



Scheme 58: Asymmetric Diels-Alder reaction catalysed by LLA.

1.6.5 Chiral Lewis Acid Complexes of Dichloroboranes

Oh and co-workers have shown how the asymmetric Diels-Alder reaction of α,β-unsaturated aldehydes with cyclopentadiene can be carried out using a complex derived from a chiral amino acid ligand and 1,8-naphthalenediylbis(dichloroborane).[90] The table below describes how changing the structure of the amine ligand or dienophile substituents affects the *endo* or *exo* selectivity of the aza Diels-Alder reaction (Table 24). The table shows that the best *exo*-selectivity was attained when an L-tryptophan ligand was used with an α-bromo-substituted aldehyde, whilst the best *endo*-selectivity was obtained from L-valine derived ligand and methacrolein as the dienophile.



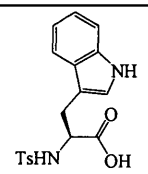
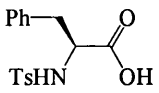
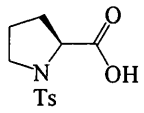
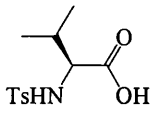
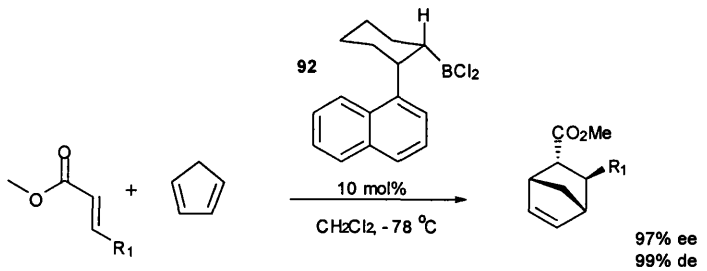
R	*Ligand*	*Exo/Endo*	*ee, %*	*Yield, %*
Br		92:8	44 (*exo*)	84
Me		63:37	20 (*exo*)	46
H		**6:94**	**62 (*endo*)**	**53**
Br		89:11	8 (*exo*)	83
H		2:98	0 (*endo*)	82
H		2:98	0 (*endo*)	84

Table 24: Diels-Alder reactions catalysed by chiral amino acid-bis(boron-dichloro) complex.

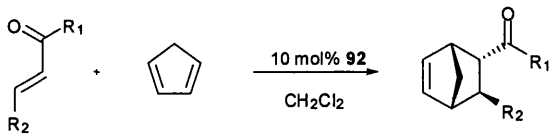
Hawkins and co-workers have designed an alternative alkyl dihaloborane Lewis acid **92** for the Diels-Alder reaction between methyl crotonate and cyclopentadiene (Scheme 59). The enantiomeric excess achieved were generally high ranging between 83-97% depending on the β-substituent of the methyl crotonate substituent.[91]



Scheme 59: Diels-Alder reaction of methyl crotonate and cyclopentadiene.

In more recent times, Hawkins *et al.* have reported that alkyl dichloroborane **92** can be used as a catalyst for Diels-Alder reaction of cyclopentadiene with various α,β-

unsaturated ketones and α,β-unsaturated acid chlorides,[92] affording cycloaddition products in up to 92% (Table 25).



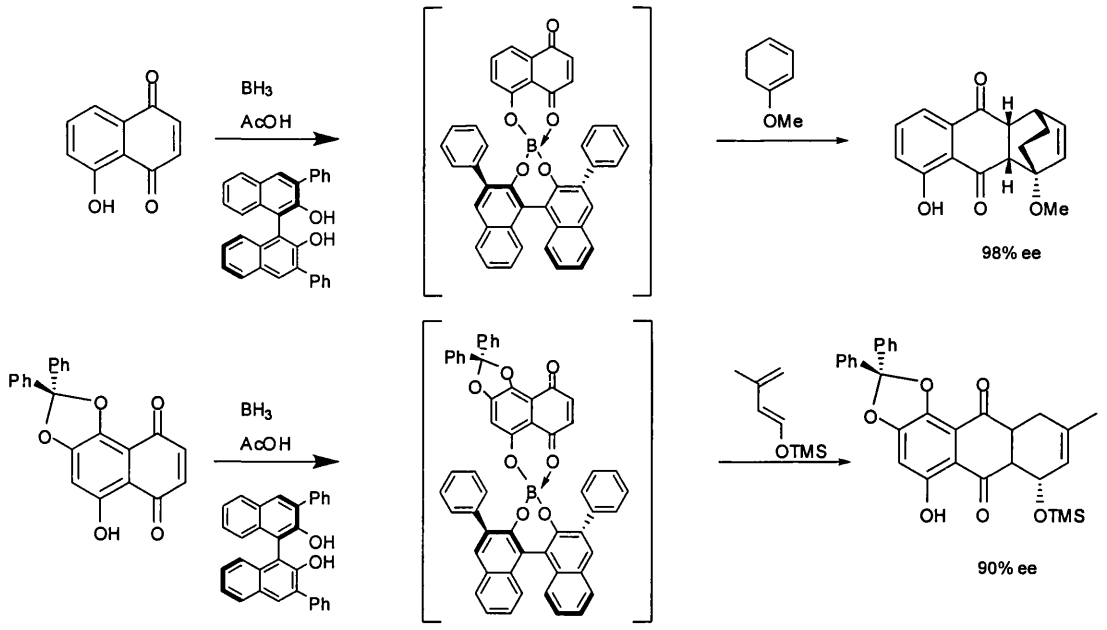
R_1	R_2	*Temperature, °C*	*Time, h*	*Endo/Exo*	*ee, %*
Me	H	- 74	1	> 100:1	81 (*endo*)
Et	H	- 78	24	> 100:1	83 (*endo*)
^{i}Pr	H	- 30	20	32:1	16 (*endo*)
Me	Me	- 30	20	32:1	71 (*endo*)
Cl	**Me**	**- 20**	**52**	**> 10:1**	**92 (*endo*)**
Cl	Et	- 18	48	> 10:1	76 (*endo*)
Cl	CH_2Br	- 18	72	> 10:1	80 (*endo*)

Table 25: Asymmetric Diels-Alder reactions catalysed by **92**.

1.6.6 BINOL-Boron Lewis Acids

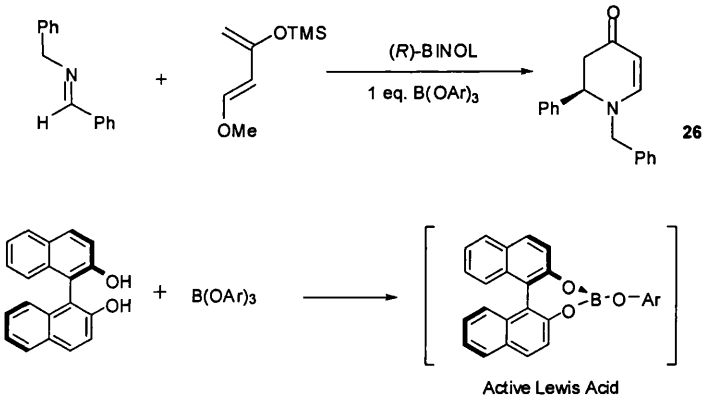
This thesis describes my investigations into developing boron-BINOL mediated asymmetric aza Diels-Alder reactions, and this section of the review focuses in detail on the research effort that has been carried out this type of catalyst for different types of reactions.

Kelly and co-workers were the first group to use boron complexed with binaphthol ligands as an asymmetric catalyst back in the mid 1980's. They demonstrated how *peri*-hydroxyquinones could be used as substrates for asymmetric Diels-Alder reaction with cyclohexadienes, using a boron-BINOL complex as a catalyst for stereocontrol (Scheme 60).[93] The boron-BINOL species responsible for asymmetric catalysis was not determined, although transition state shown was proposed, however, good ee's were demonstrated for the reaction of 1-methoxycyclohexa-1,3-diene (98% ee) or trimethyl-(3-methyl-buta-1,3-dienyloxy)-silane (90% ee).



Scheme 60: Diels-Alder reaction of *peri*-hydroxyquinones.

Yamamoto *et al.* then described the asymmetric aza-Diels-Alder reaction of an imine mediated by an *in situ* generated chiral boron-BINOL complex generated *in situ* (Table 26).[23]



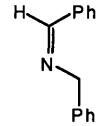
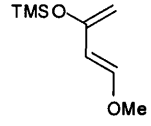
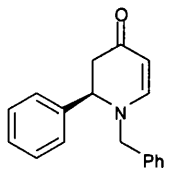
Imine	*Diene*	*Ar (B(OAr)3)*	*Temp, °C*	*ee, %*
		Phenyl	- 78	82
		Phenyl	- 100	85
		2-tolyl	- 78	84
		3,5-xylyl	- 78	86

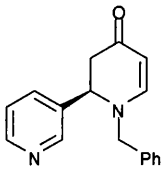
Table 26: Asymmetric aza Diels-Alder reaction mediated by different boron-BINOL reagent.

The chiral boron-BINOL reagents were readily formed by mixing triaryl borate and 1 eq. (*R*)-binaphthol in methylene chloride. Subsequent addition of aldimine and Danishefsky's diene resulted in the formation of chiral dihydropyridone **26** with good enantiomeric purity (Table 27).

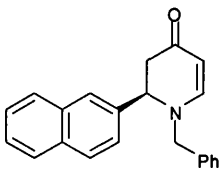
This aza Diels-Alder methodology was then applied to the synthesis of a range of further imine substrates, with boron-BINOL complexes catalysing the formation of a series of dihydropyridones 1-10 in poor to excellent ee.



26



93



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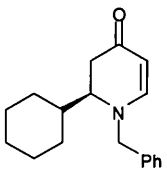

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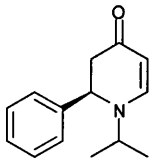

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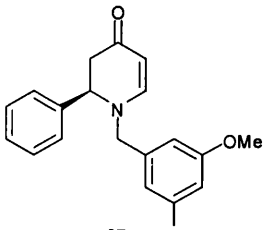

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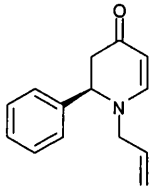

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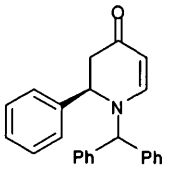

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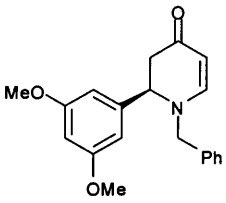

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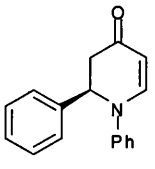


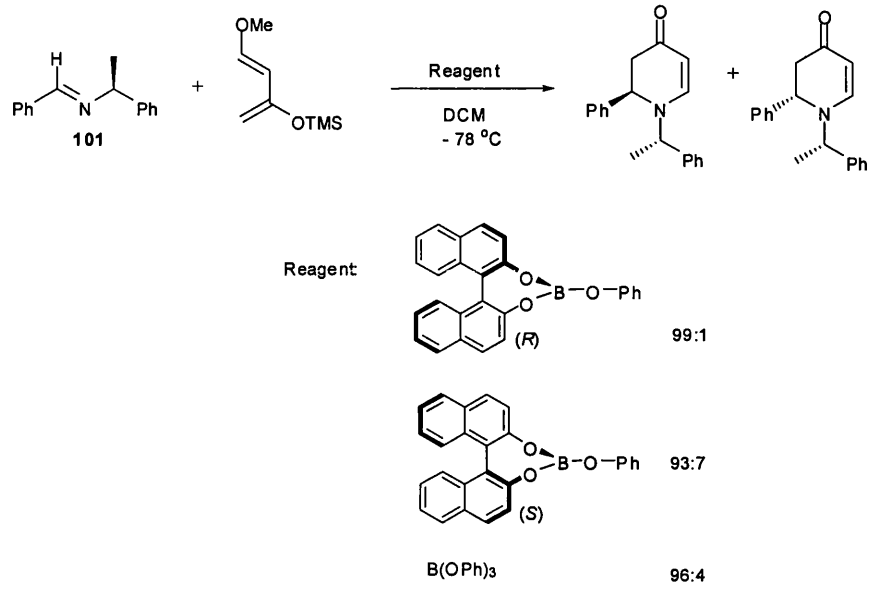
100

Dihydropyridone	*Yield, %*	*ee, %*
26	75	82
93	71	90
94	83	84
95	45	76
96	13	4
97	73	85
44	97	70
98	trace	Not Determined
99	89	72
100	77	24

Table 27: Asymmetric aza-Diels-Alder reactions affording different dihydropyridones.

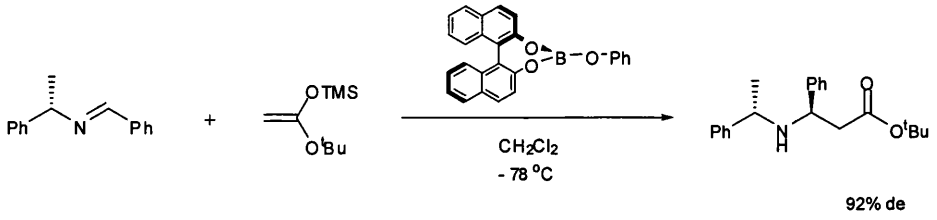
Yamamoto also investigated the aza Diels-Alder reaction of imines containing an α-methyl benzylimine chiral auxiliary fragment and found that the resultant

dihydropyridones were formed in very high de, presumably under the matched control of the boron-BINOL catalyst and the chiral auxiliary fragment (Scheme 61).



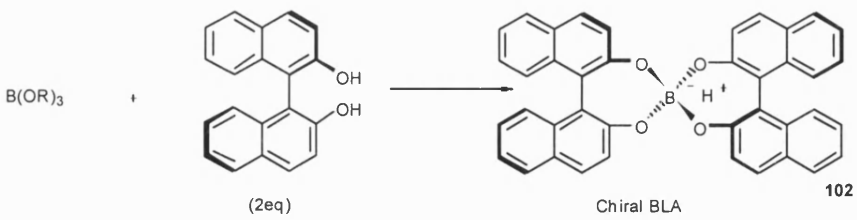
Scheme 61: Double asymmetric induction of aza-Diels-Alder reaction mediated by a chiral boron-BINOL reagent.

This type of boron-BINOL reagent has also been applied to Mannich-type reactions for the formation of β-amino esters via addition of a silyl ketene acetal to α-methyl benzylimines to afford a major diastereomer with a high degree of selectivity (Scheme 62).[94]



Scheme 62: Mannich-type reaction of chiral imine and silyl ketene acetal.

Yamamoto subsequently reported the use of a different boron-BINOL complex for these type of aza-Diels-Alder and Mannich reactions.[25] The complex was prepared in a similar manner to that used previously, except that a 1:2 molar ratio of trialkyl borate to binaphthol was used for its formation (Scheme 63).



Scheme 63: Boron-BINOL complex as a Bronsted acid-assisted chiral Lewis acid.

This chiral boron Lewis acid BLA **102** was formed in situ by mixing 2 equivalents of BINOL with 1 equivalent of trimethyl borate in methylene chloride for one hour. Evidence for the structure of the chiral BLA was obtained by carrying out X-ray crystal diffraction on crystals that were obtained from mixing $B(OPh)_3$, imine **101** and BINOL. These crystals were found to be comprised of a 1:2:1 molar ratio of boron, BINOL and imine in the presence of a molecule of phenol in the crystal lattice.

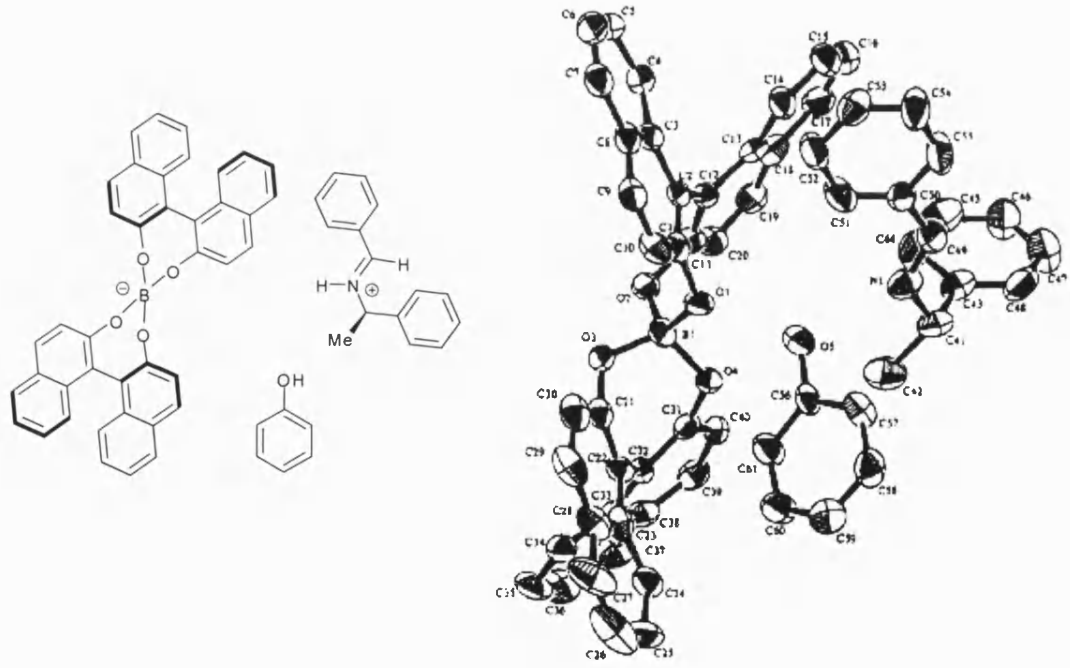
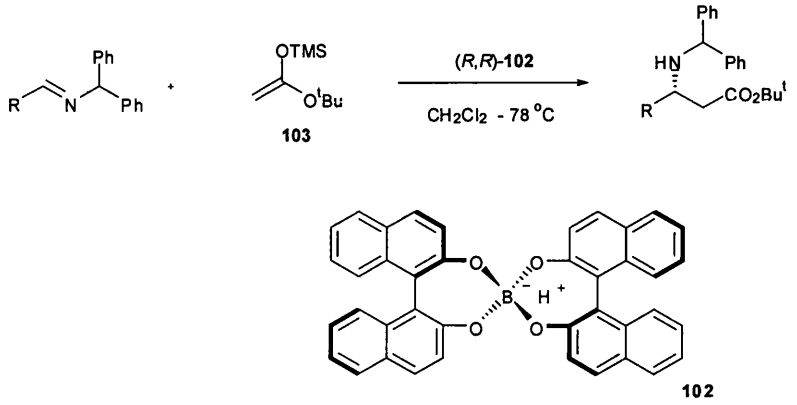


Figure 22: ORTEP diagram of X-Ray crystal structure of (*S*)-**102**-**101**-PhOH.CH_2Cl_2

These crystals were then employed as catalysts for diastereoselective Mukiyama aldol and aza Diels-Alder reactions, affording aldol and dihydropyridin-2-one products in very high de, which suggests that this species is either the catalyst, or a precatalyst in these asymmetric reactions.

In general chiral reagent **102** was found to be a more efficient chiral catalyst than the monomeric BINOL-boron reagent originally proposed to contain only one binaphthol ligand. Enantioselective Mannich reactions of *N*-benzhydrylimines with silyl ketene acetal **103** in the presence of BLA **102**, were shown to proceed with high enantioselectivity, if somewhat moderate yields at – 78 °C (Scheme 64/ Table 28).



Scheme 64: Mannich reaction using *N*-benzhydrylimines.

R	*Yield, %*	*ee, %*
C_6H_5	58	96
p-MeC_6H_4	35	97
***p*-ClC_6H_4**	**45**	**98**
p-$AcOC_6H_4$	52	98
2,4-$Cl_2C_6H_3$	49	95
2-Naphthyl	43	96

Table 28: Enantioselective Mannich reactions of *N*-benzylhydylimines using reagent **102**.

The enantioselectivity of the Mannich reactions shown in Table 28 were higher due to the presence of the bulky *N*-diphenylmethane substituent of the benzhydrylimine substrates, with the best result being obtained for the *para*-chloro phenyl imine derivative. The *N*-diphenylmethyl protecting group was easily cleaved under hydrogenolysis conditions producing a favourable synthesis of β-aryl-β-amino acids in enantiomerically pure form, which are key fragments of spermine alkaloids.[95]

The nature of the catalytic species was studied in solution using nOe experiments, and as a result an imine complex (*R*)-**102**.(*S*)-101 was proposed as the reactive species. This complex was comprised of the imine substrate coordinated to a central boron atom coordinated to two equivalents of BINOL, with an intramolecular hydrogen bond being responsible for controlling the overall conformation of the complex. This intramolecular

hydrogen bond was proposed to orientate the reactive species into a conformation that effectively blocks the *Si* face of the imine so that the incoming nucleophile is forced to approach from the *Re* face as drawn in Figure 23.

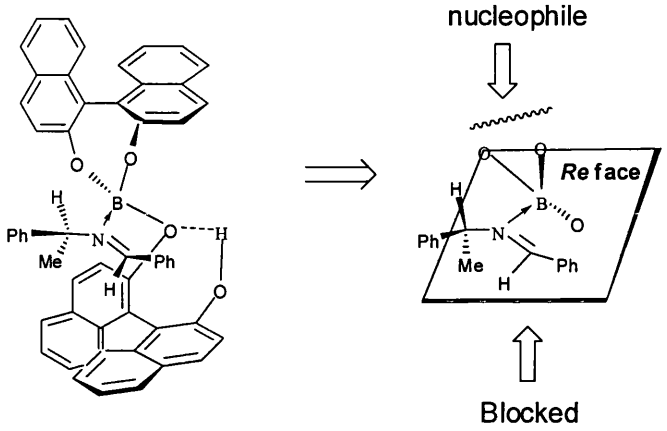
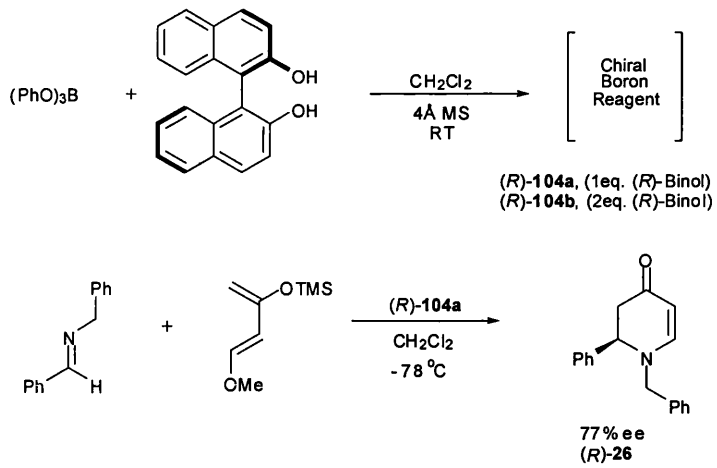


Figure 23: Matched pair complex (*R*)-**102**.(*S*)-**101**.[25]

Research in the SDB and TDJ groups has focused on mechanistic issues of these type of boron-binaphthol catalysed asymmetric reactions, directed towards determining the true identity of the chiral boron reagent created when one or two equivalents of binaphthol are mixed with alkyl borates. Yamamoto *et al.* initially suggested that the likeliest species was a monomeric boron-BINOL complex (synthesised using 1 eq. of BINOL),[24] however they subsequently reported on a dimeric 'ate' BLA species **102** (synthesised from 2 eq. of BINOL) as the active species.[25]

Non-linear effects in asymmetric catalysis have often been employed as a useful tool for probing whether an enantioselective catalytic species contains 2 or more equivalents of a chiral ligand. Therefore, it was investigated whether boron-BINOL complexes prepared using scalemic binaphthol, would result in a non-linear effect when derived complexes were employed to catalyse an aza-Diels-Alder reaction.[26]

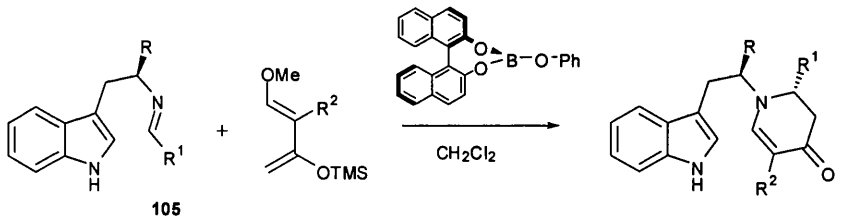


Scheme 65: Aza Diels-Alder reaction employing unknown chiral boron reagents **104a** and **104b**.

The reaction conditions repeated in Scheme 65 were identical to those employed by Yamamoto and co-workers, however the results obtained showed a slightly inferior enantiomeric excess (77 % ee compared with 82 % ee in the original report). This aza-Diels-Alder reaction was then repeated four times at – 78 °C using a chiral boron reagent **104a** formed from 1 eq. of BINOL of varying enantiopurity (0 - 80% ee). The results showed that a positive non-linear effect was observed, thus indicating that the active catalyst in these reactions contained more than one equivalent of (*R*)-BINOL.

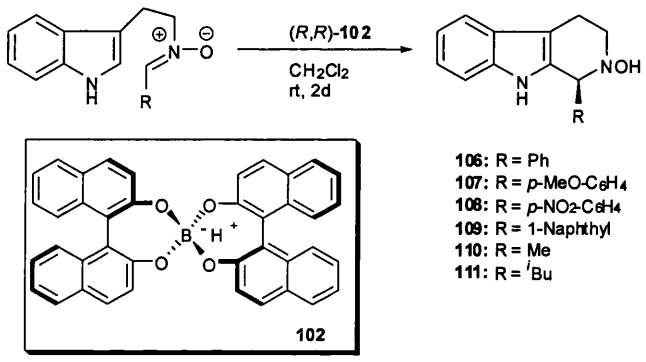
As a result, non-linear effects in the same aza Diels-Alder reaction were then investigated in the same reaction using a chiral boron reagent **104b** that was prepared using two equivalents of (*R*)-BINOL. The use of scalemic BINOL for the formation of **104b** gave an even greater positive non-linear effect, adding further evidence that the chiral boron reagent in these reactions contains at least two equivalents of BINOL.

Waldman and co-workers subsequently used Yamamoto's boron-BINOL Lewis acid in a Mannich-Michael (formal aza-Diels-Alder) reaction as part of a wider synthesis of Reserpine type alkaloids.[96] They employed a boron-BINOL complex to achieve high selectivity for the diastereoselective reaction of the indole derived imine **105** with a functionalised Danishefsky's diene (Scheme 66).



Scheme 66: Mannich-Michael type reaction of Schiff base and diene.

Nakagawa *et al.* utilised Yamamoto's BLA **102** in their enantioselective Pictet-Spengler reaction of a series of nitrones resulting in compounds **106 - 111** in moderate to high ee (Table 29).[97]



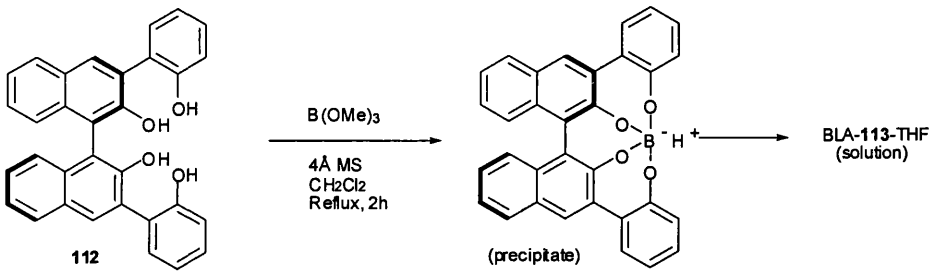
Indole	*Yield, %*	*ee, %*	*R/S*
106	81	73	*S*
107	39	91	*S*
108	75	74	*S*
109	59	31	*S*
110	94	15	*R*
111	68	50	*S*

Table 29: Pictet-Spengler reactions of nitrones catalysed by BLA.

Yamamoto and co-workers then developed a second generation class of boron-BINOL based BLA's for asymmetric Diels-Alder reaction. They recognised that higher levels of asymmetric induction might be achieved if appropriate π-π donor-acceptor interactions between a dienophile and chiral ligand could be introduced into the

transition state and as a consequence a series of new BLA's were developed as improved catalysts for highly *exo* selective Diels-Alder reactions.

The first of these BLA's employed (*R*)-3,3'-di(2-hydroxyphenyl)-2,2'-dihydroxy-1,1'binaphthol **112** as a ligand, whose reaction with trimethyl borate afforded a white solid, that was subsequently dissolved in THF to afford BLA-**113** (Scheme 67).[25]



Scheme 67: Formation of BLA **113**.

5 mol% of BLA-**113**-THF catalysed the Diels-Alder reaction between α-bromoacrolein and various dienes (Table 30) to afford Diels-Alder adducts with very high *exo*-selectivity. This BLA was found to be limited to using α-substituted α,β-enals, since dienophiles without a substitutent at their α position gave poor stereocontrol (<40%).

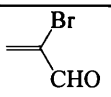
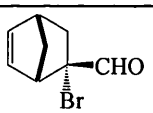
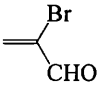
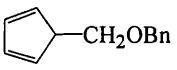
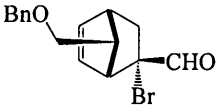
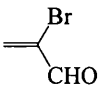
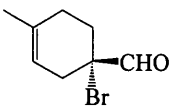
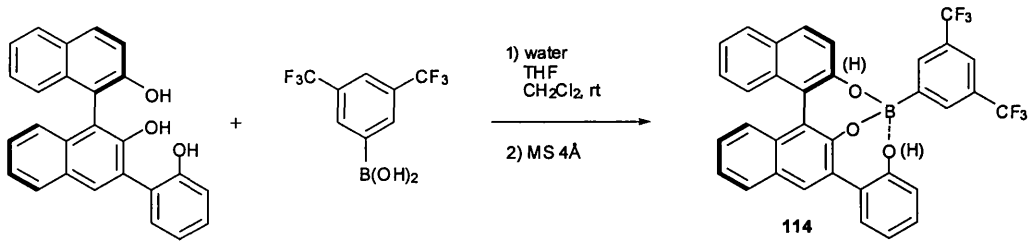
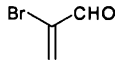
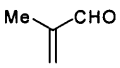
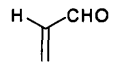
Dienophile	*Diene*	*Product*	*Exo/endo*	*ee, %*
			99:1	99 (*exo*)
			99:1	94 (*exo*)
			N/A	94

Table 30: Enantioselective Diels-Alder reaction catalysed by BLA-**113**.

Yamamoto *et al.* then developed a new trifluoromethyl substituted boron-BINOL based BLA **114** (Scheme 68), which had both enhanced Lewis acidity and catalytic activity, enabling successful Diels-Alder reactions of α-unsubstituted α,β-enals to be carried out with a whole host of dienes (Table 31).[98]



Scheme 68: Synthesis of BLA **114**.

Dienophile	*Diene*[a]	*Mol %*	*Yield, %*	*ee, %.*
	**CP**	**5**	**> 99**	**> 99**
	CP	1	97	97
	CH	10	65	95
	DMB	10	95	91
	IP	**10**	**95**	**> 99**
	CH	20	87	95
	DMB	10	81	> 99
	IP	10	95	99
	CP	5	84	95
	CH	10	> 99	96
	DMB	**10**	**97**	**> 99**
	IP	10	95	99

a) CP = cyclopentadiene. CH = 1,3-cyclohexadiene. DMB = 2,3-dimethylbutadiene. IP = Isoprene

Table 31: Enantioselective Diels-Alder reaction catalysed by (*R*)-BLA-**114**.

A final BLA designed for the asymmetric Diels-Alder reaction was reported by the Yamamoto group in 1998,[99] whereby bis[3,5-bis(trifluoromethyl)phenyl]boronic acid was complexed to BINOL's **115a-d** to afford the BLA's **116a-d** that were used as catalysts for the Diels Alder reaction betweeen methacrolein and cyclopentadiene (Figure 24).

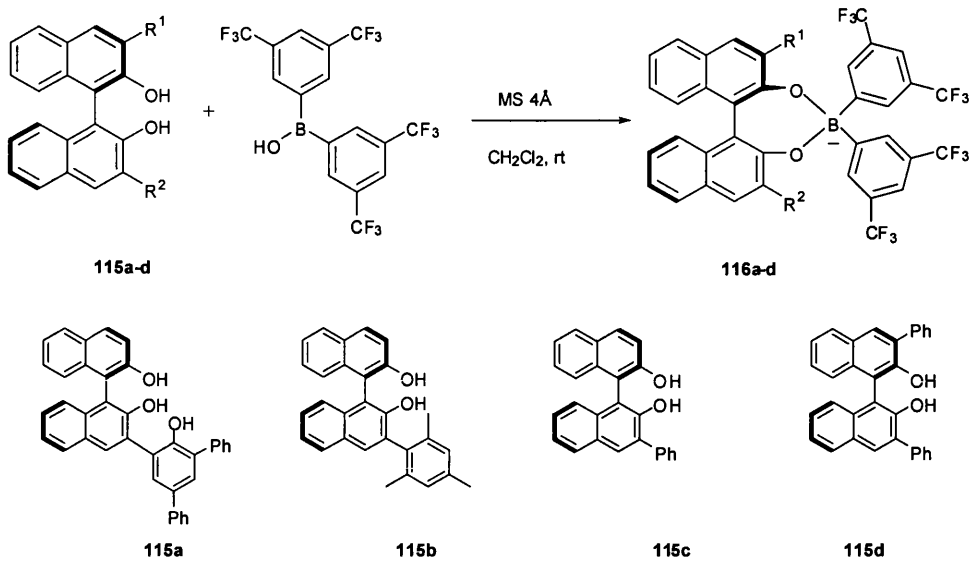
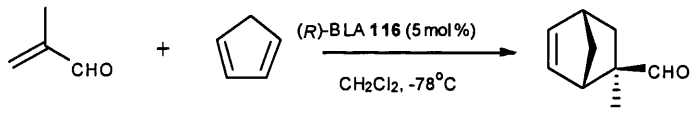


Figure 24: Synthesis of BLA's **116-d**.

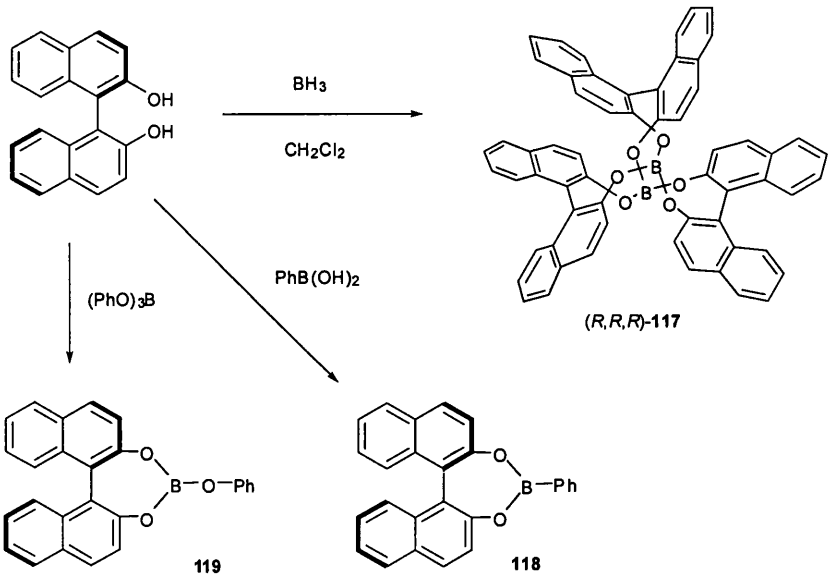
The best results were obtained using BLA **116a** which gave an ee of 86% for the formation of the cycloadduct, which was a slight increase on the previous levels of stereocontrol obtained using BLA **114**. Further results are outlined in Table 32 below:



Chiral BLA	*Exo/Endo*	*ee, %*	*Configuration*
116a	**94:6**	**86**	***R***
114	**95:5**	**80**	***R***
116b	95:5	55	*R*
116c	92:8	49	*R*
(*R*)-BINOL	89:11	15	*R*
116d	90:10	1	*R*

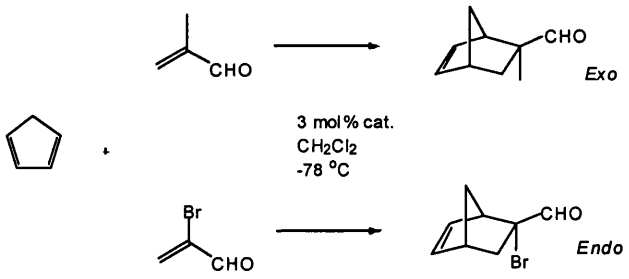
Table 32: Modification and preparation of Diels-Alder catalysts.

Kaufmann and co-workers have independently developed several other types of boron-BINOL complexes as Lewis acids for the asymmetric Diels-Alder reaction.[100] Complex **117** was formed when BINOL was reacted with borane in a 3:2 ratio (Scheme 69), however they report that reaction of phenylboronic acid or triphenylborate with BINOL resulted in monomeric complexes **118** and **119** respectively.



Scheme 69: Boron-BINOL complexes of β-binaphthol and various borane reagents.

These boron-BINOL complexes were used to catalyse the stereoslective Diels-Alder reaction of cyclopentadiene and α-substituted α,β-enals (Scheme 70).



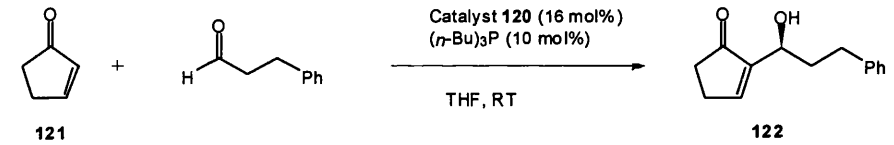
Scheme 70: Diels-Alder reaction of α-substituted α,β-enals using boron-BINOL reagents.

The use of the C_3-symmetric propeller compound **117,** where the BINOL ligands effectively form propeller like blades, showed good *exo* selectivity for reaction of cyclopentadiene with methacrolein (96:4), and good *endo* selectivity for the reaction with bromoacrolein (94:6). Species **119** gave identical selectivity in this reaction, however monomeric species **118** showed lower selectivities especially when bromoacrolein was used as a dienophile (Table 33).

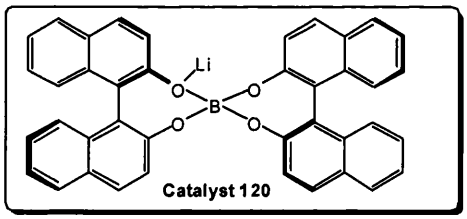
Catalyst	*Yield, %* *(methacrolein)*	*Yield, %* *(bromacrolein)*	*Exo/Endo* *(methacrolein)*	*Exo/Endo* *(bromacrolein)*
117	90	51	96:4	6:94
118	80	48	93:7	10:90
119	91	56	96:4	6:94
No cat.	5	38	86:14	22:78

Table 33: BINOL-boron complexes used for the stereoselective synthesis of methacrolein and bromacrolein.

Sasai *et al.* have developed a new doubly activated catalyst for the Morita-Baylis-Hillman reaction using principles first developed by Shibasaki *et al.*[101] They used a heterobimetallic boron-lithium-bis(binaphthoxide) **120**, prepared from BH_3.THF (16 mol%), *n*-BuLi (16 mol %) and BINOL (32 mol %) to catalyse reaction of cyclopenteneone **121** using a Lewis base (n-Bu)$_3$P (10 mol %) to facilitate formation of β-hydroxy-ketone **122** in quantitative yield and in 46 % ee (Scheme 71).[102]

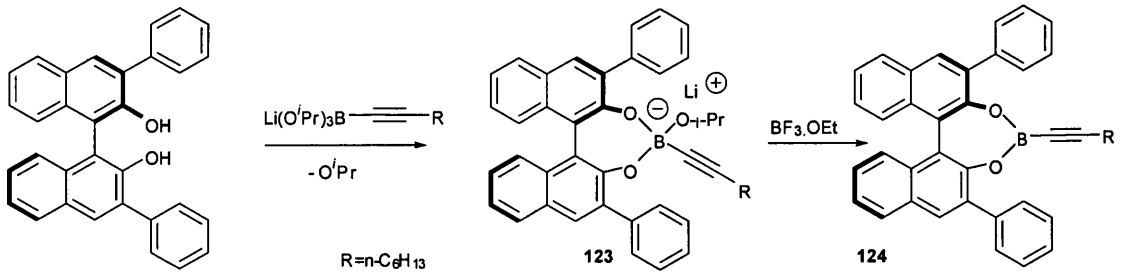


121 122



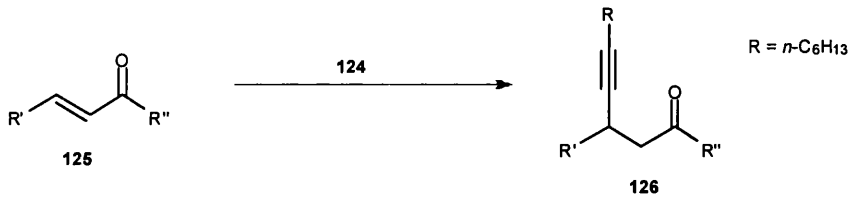
Scheme 71: Enantioselective Morita-Baylis-Hillman reaction promoted by heterobimetallic catalyst **120**.

Chong and colleagues have employed an alkynyl-boron-BINOL complex which they used to catalyse asymmetric conjugate addition of alkyne fragments to enone acceptors.[103] The chiral boron-BINOL reagent was synthesised via reaction of a lithium-alkynylboronate with a binaphthol type ligand to afford **123,** which was then converted to the desired alkynylboronate **124** via the addition of boron trifluoride etherate (Scheme 72).



Scheme 72: Synthesis of chiral alkynylboronates.

Reaction of this catalytic species with a series of enones **125a-g** resulted in the formation of a series of β-alkynyl ketones in 74 – 98% ee (Table 34).



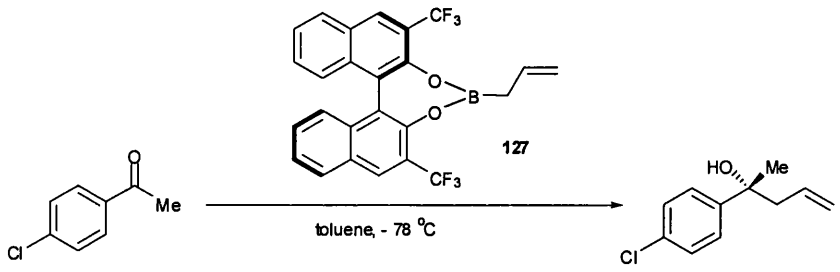
a: R' = R'' = Ph
b: R' = Ph, R'' = Me
c: R' = *t*-Bu, R'' = Ph
d: R' = *E*-CH$_3$CH=CH, R' = Ph
e: R' = 2-furyl, R'' = Ph
f: R' = 1-naphthyl, R'' = Ph
g: R' = R'' = *p*-BrC$_6$H$_4$

enone	*product*	*Yield, %*	*ee, %*
125a	**126a**	88	85
125b	**126b**	50	85
125c	**126c**	87	82
125d	**126d**	82	74
125e	**126e**	**91**	**98**
125f	**126f**	**91**	**95**
125g	**126g**	93	75

Table 34: Enatioselective conjugate addition of alkynyl groups to enones.

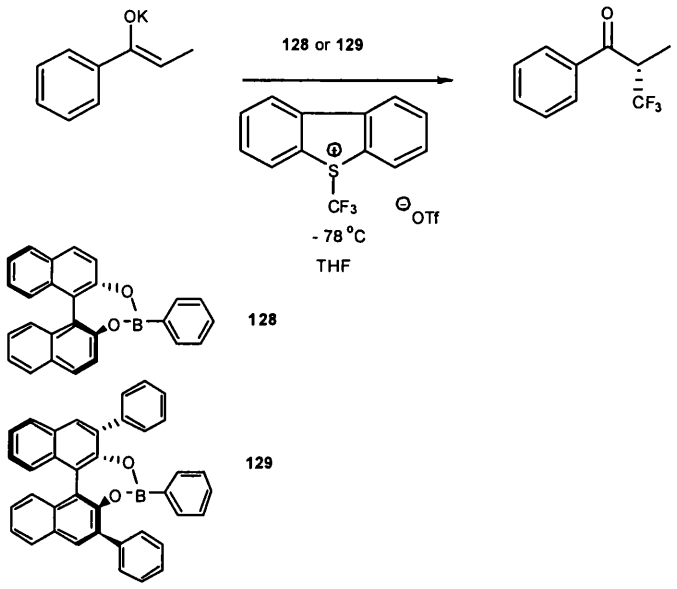
In a more recent paper Chong *et al.*, used chiral allyl boronates derived from 3,3'-substituted BINOL's for the asymmetric allylation of benzaldehyde. The use of a BINOL ligand containing trifluoromethyl groups at the 3 and 3' positions gave

secondary alcohols in up to 96% ee. The most interesting results were obtained using this catalyst for the allyl boration of ketones, since unsymmetric ketone substrates gave tertiary alcohols in very high ee. The best results obtained came from using *p*-chloroacetophenone which gave its corresponding tertiary alcohol in 98% ee (Scheme 73).[104]



Scheme 73: Asymmetric allylboration of ketones using boronate **127**.

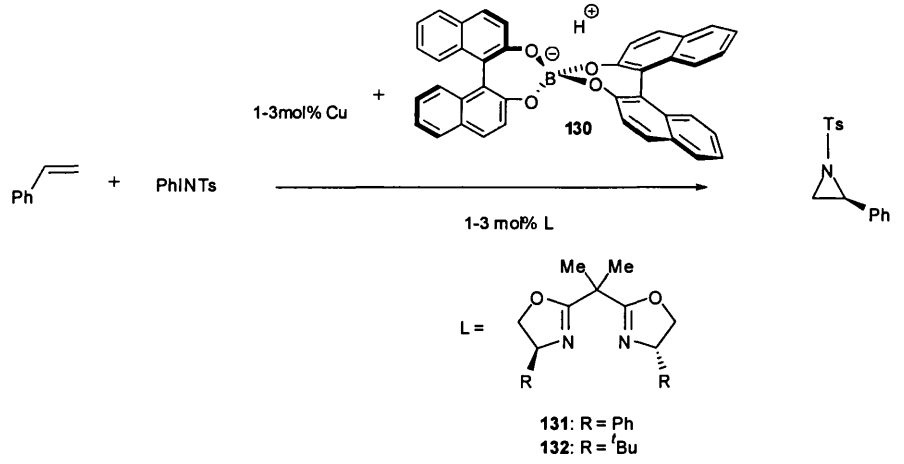
A new method of enantioselective trifluoromethylation of potassium enolates of ketones has been reported by Umemoto and colleagues, who generated boron-BINOL complexes **128** and **129** *in situ* to induce enantioselectivity in the transfer of a trifluoromethyl group from (*S*)-(trifluoromethyl)dibenzothiophenium salts.[105] The yields and enantioselectivities obtained were not particularly high, however, this is a highly original approach for the trimethylation of enolates which is a difficult asymmetric transformation to achieve (Scheme 74).



Boron Complex	*Yield, %*	*ee, %*
128	62	12
129	54	45

Scheme 74: Triflormethylation of enolates using boron-BINOL complexes.

In a new method to introduce chirality Arndsten *et al.* attempted to use an enantiopure boron-BINOL complex as a chiral weakly coordinating anion, to catalyse the enantioselective copper-catalysed aziridination of styrene. Their initial work involved aziridination of styrene using copper complexes containing counter ions such as OTf^- and ClO_4^- in the presence of bis(oxazoline) ligands in benzene. Very poor enantioselectivities were observed in these reactions, however when the chiral counter[106] ion **130** was added to the reaction then modest enantioselectivities 22% ee were achieved (Table 35).[107]

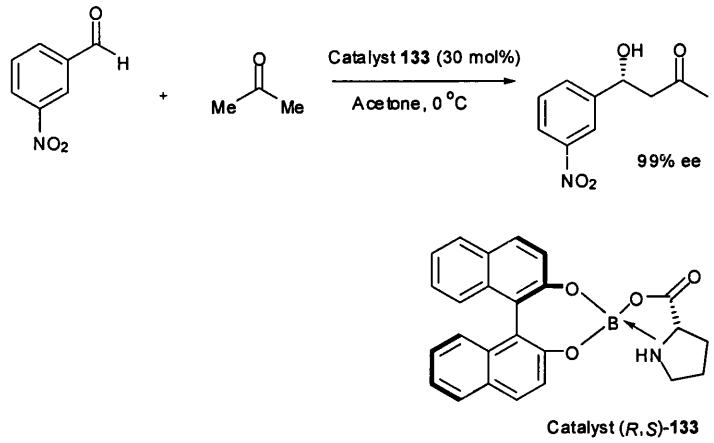


Ligand	*Counter ion*	*Solvent*	*ee, %*	*Yield, %*[a]
(*R*)-**131**	(*S*)-**130**	benzene	22	75
(*R*)-**131**	(*R*)-**130**	benzene	24	85
(*S*)-**132**	(*S*)-**130**	benzene	13	nd
(*S*)-**132**	(*R*)-**130**	benzene	12	nd
none	(*R*)-**130**	benzene	7	86
none	(*S*)-**130**	benzene	7	88
None	(*R*)-**130**	CH_2Cl_2	4	97
none	(*R*)-**130**	MeCN	1	87

a) nd = not determined.

Table 35: Aziridination of styrene using chiral boronate anion approach.

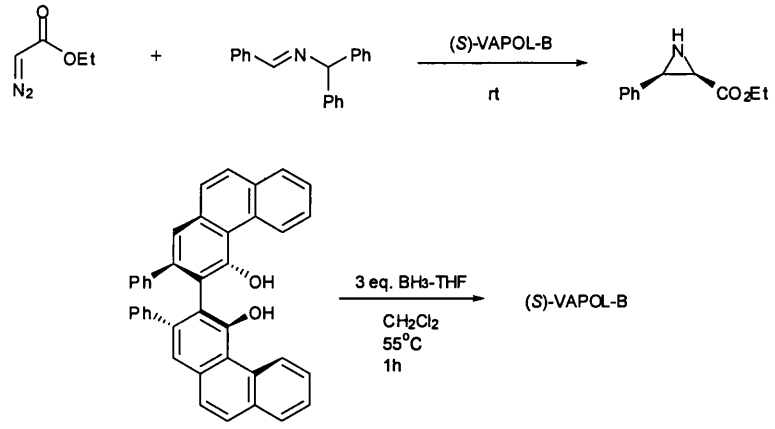
Shan *et al.* have recently developed a spiroborate ester derived from boric acid, (*R*)-BINOL and L-proline as a catalyst for the highly enantioselective aldol reaction of acetone and 3-nitrobenzaldehyde, achieving an ee of 99% and a yield of 92% at 0 °C over a 50 h time period (Scheme 75).[108]



Scheme 75: Spiroboronate **133** catalysed asymmetric aldol reaction.

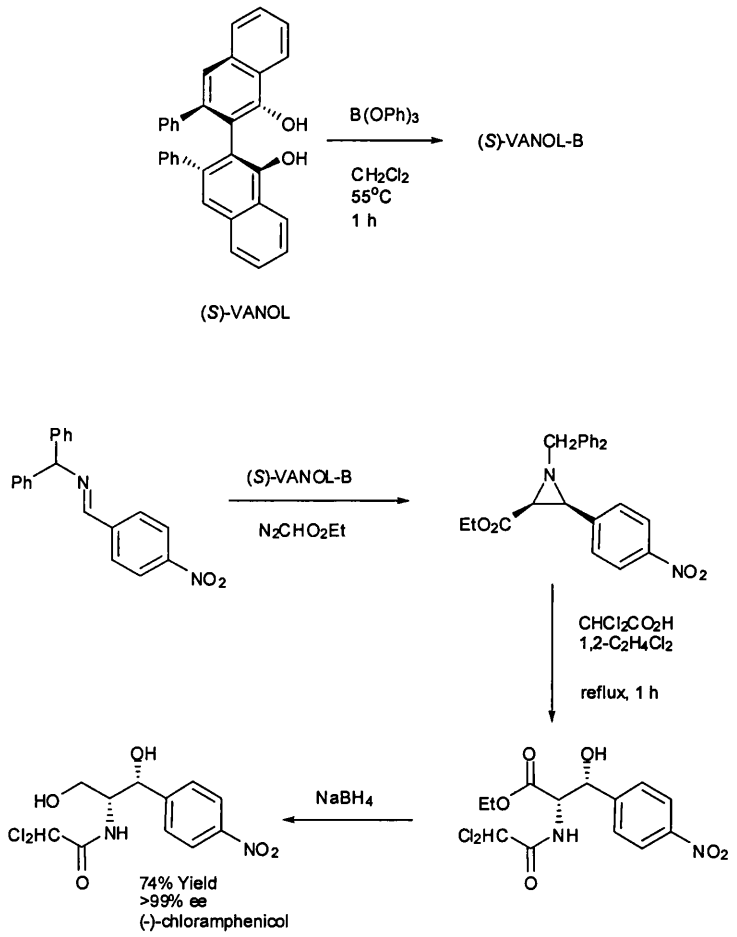
1.6.7 Chiral Boron Complexes of Vaulted Biaryls

Wulff and co-workers have introduced the use of boron-VAPOL complexes as chiral Lewis acid catalysts for the asymmetric aziridination of benzhydryl imines with ethyl diazoacetate. These catalysts are easily prepared by heating (*S*)-VAPOL with borane-THF complex in methylene chloride. The reaction, as shown in Scheme 76, afforded the *cis*-aziridine in 74% yield and an ee of 98%. The selectivity of this aziridination reaction was also very good with the *cis* isomer being favoured in a ratio of 50:1. The enantioselectivity of the *cis*-aziridine was not a function of the substrate to catalyst ratio which remained constant when the catalytic loading was reduced from 10 to 1 mol%, however the rate of reaction did drop significantly when the loading was below 2.5%.[109]



Scheme 76: Asymmetric aziridination catalysed by (*S*)-VAPOL-B.

This class of aziridination reaction was later used for the total synthesis of the antibiotic (-)-choramphenicol which could be synthesised in four steps starting from *p*-nitro-benzaldehyde (Scheme 77).[110] Several ligands were used for the asymmetric aziridination step including BINOL, BANOL and VAPOL, with the best results arising from the use of (*S*)-VANOL, which gave a selectivity of 50:1 (*cis*) and an enantiomeric excess of 91%.



Scheme 77: Synthesis of chloramphenicol using an asymmetric aziridination step.

1.6.8 Concluding remarks

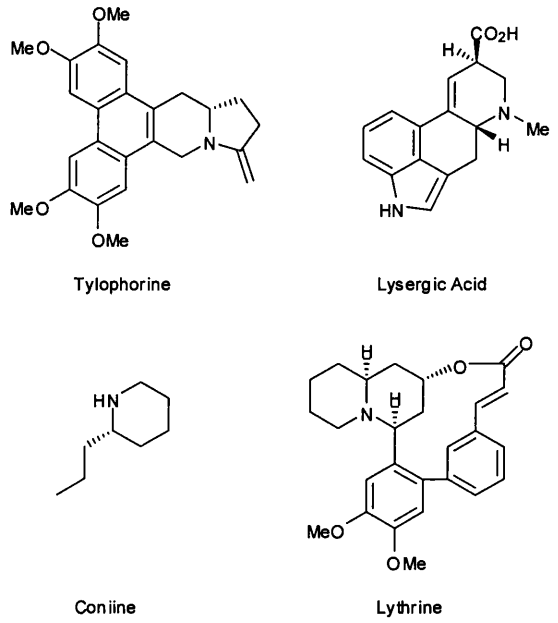
Chiral boron Lewis acid catalysts are clearly 'state of the art' reagents in asymmetric synthesis given their application in a wide range of synthetic transformations and their relative inexpensive cost. Much work has been carried out over the last fifteen years to optimise their performance and with the field of asymmetric homogeneous catalyst ever growing it is clear that further novel boron complexes for asymmetric catalysis will

appear in the near future. This introduction has served to set the scene for the results and discussion chapters of this thesis that deal with the development of potential boron-BINOL Lewis acid catalysts for asymmetric aza Diels-Alder reactions and the application to natural product synthesis.

2 Results and Discussion 1: Initial Investigations into the Boron-BINOL mediated aza Diels-Alder reaction

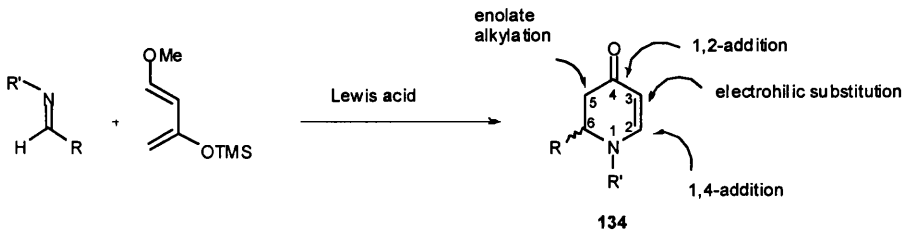
2.1 Introduction

The main aim of this research project was to devise a synthetically useful aza Diels-Alder synthesis employing reaction conditions suited to both industry and academia. One of the most common aza Diels-Alder reactions uses aldimines and an activated diene known as Danishefsky's diene. This reaction produces 2,3-dihydro-4-pyridones (such as **134**) that represent attractive building blocks for alkaloid synthesis.[19-21,24]



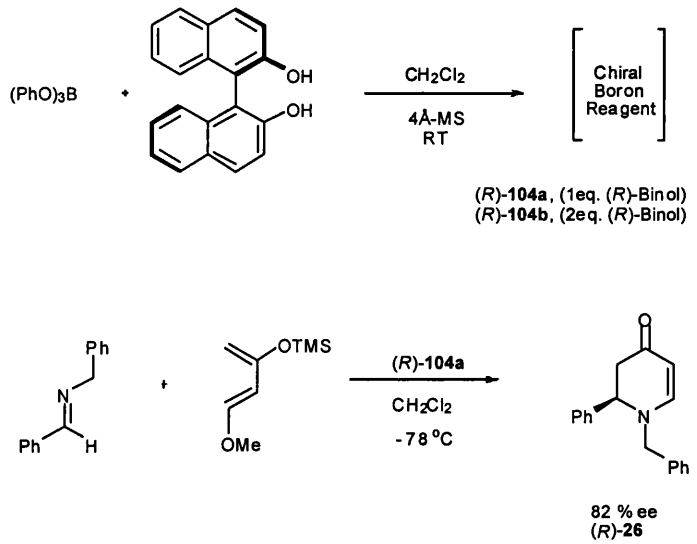
Scheme 78: Alkaloids which could potentially be synthesised from pyridone intermediates.

These type of dihydropyridones can be manipulated synthetically in a number of ways including 1,4-conjugate addition of nucleophiles to the enone moiety followed by trapping of the resultant enolate at C3, nucleophilic 1,2 addition to the enone carbonyl, whilst enolate formation could allow for selective alkylation at the C5 position (Scheme 79).[111]



Scheme 79: Aza Diels-Alder reaction of imine and Danishefsky's diene results in the formation of pyridone heterocycles that are versatile synthons for alkaloid synthesis.

One of the most promising systems that maybe employed for the asymmetric aza Diels-Alder reaction are the boron-BINOL chiral Lewis acids developed by Yamamoto.[23,24] This system has the advantage of using cheap starting materials, is very simple to execute and is suitable to a wide range of substrates when compared to other literature examples.[112] The system employs the use of an alkyl or aryl borate premixed in solution with BINOL to form an active species which catalyses the asymmetric aza Diels-Alder reaction as shown in Scheme 80. This system requires stoichiometric amounts of BINOL and borate to form the active catalyst, which is clearly non-ideal when compared to other catalytic systems that can function at lower catalyst loadings.



Scheme 80: Boron catalysed asymmetric aza Diels-Alder reaction developed by Yamamoto *et al.*

The figure below highlights the range of pyridones synthesised previously by Yamamoto using his boron-BINOL system to catalyse different aza Diels-Alder reactions at – 78 °C. Generally the best levels of asymmetric induction occurred when imines derived from aromatic aldehydes were employed (Figure 25).

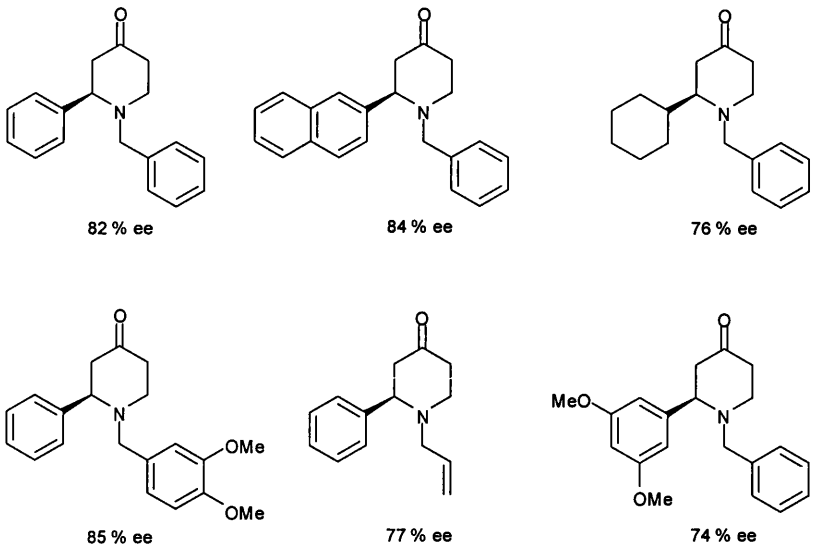


Figure 25: Dihydropyridones synthesised by Yamamoto *et al.* - 78 °C.

The chiral boron-BINOL catalytic species used by Yamamoto, and others, for the aza Diels-Alder synthesis of dihydropyridones have never been properly characterised, with Yamamoto speculating on the existence of two different catalytic species depending on whether one or two equivalents of BINOL were used for catalyst formation.[113] Therefore, either an sp^2 monomeric species comprised of one equivalent BINOL, or an sp^3 dimeric 'ate' species comprised of two equivalents of BINOL have been proposed to be responsible for stereocontrol (Figure 26).

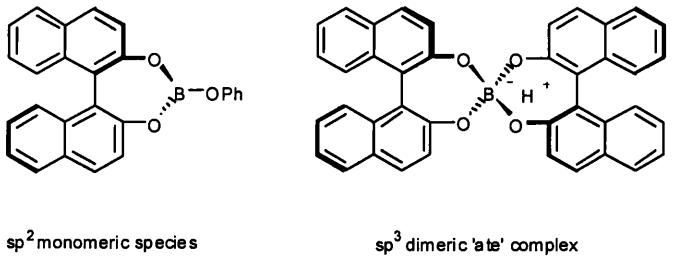


Figure 26: Yamamoto's two possible forms for the chiral boron-Binol catalyst.

The evidence for the existence of monomeric sp^2 species appears from previous literature precedent, most notably by Kaufmann *et al.* who described the use of the sp^2 species as an efficient Lewis acid for the stereoselective Diels-Alder reaction of cyclopentadiene and methacrolein.[100] They did not provide any concrete evidence for the formation of this monomeric boronate however, other than ^1H NMR and ^{11}B NMR spectroscopy which on closer analysis were inconclusive. On the other hand, the dimeric ate species has been crystallised from a dichloromethane-hexane bilayer and the

structure proven via X-ray crystallography and mass spectrometry. Yamamoto *et al.* have also crystallised a complex containing a 1:1:1 ratio of dimeric ate species, imine and phenol (added to the mixture).[113]

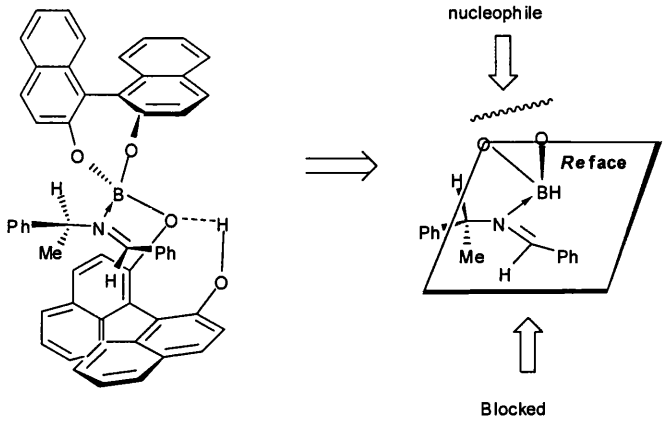


Figure 27: Yamamoto's proposed transition state when BINOL-boron reagent is complexed with imine.

The aim of this chapter was to further elucidate the nature of the complexes formed when borate and BINOL are mixed in CH_2Cl_2 under conditions normally employed for asymmetric aza Diels-Alder reactions. This would potentially allow the boron-BINOL catalyst to be redesigned with the aim of developing a more efficient catalyst that might offer the potential for high levels of asymmetric induction at room temperature, affording good enantiocontrol for a range of substrates, whilst enabling sub-stoichiometric quantities of catalyst to be used.

Work within our own research group studying non-linear effects had already revealed that at least two equivalents of BINOL ligand were present within the boron-BINOL catalyst and had shown that the monomeric species containing one equivalent of BINOL ligand were unlikely to be responsible for stereocontrol in these asymmetric aza Diels-Alder conditions.[26] It was therefore decided to carry out further investigations into the nature of these active asymmetric complexes in order to develop a fuller understanding of this catalyst system. This chapter therefore describes investigations into determining the Lewis acidity of boron-BINOL complexes employing ^{1}H and ^{11}B NMR spectroscopic studies and mass spectroscopy to determine the structure of boron-BINOL complexes. Finally, having investigated the various properties of the boron-BINOL catalytic complexes, the synthesis of model sp^3 boron-BINOL-imine complexes has been carried out whose reactivity were examined in aza Diels-Alder and Mannich type reactions.

2.2 Lewis Acidity Measurements

There are various method used for measuring Lewis acidity, which normally use spectroscopic methods such as NMR and IR for determination.[114-116] Given that Yamamoto described that boron-BINOL complexes acted as a Lewis acid to promote the aza Diels-Alder of Danishefsky's diene and an imine it was deemed important to determine its Lewis acidity. For this reason we examined the Lewis acidity of boron-BINOL complexes using a popular method based on phosphorous NMR spectroscopy.

2.2.1 Gutmann's Method

The Gutmann ^{31}P spectroscopic method was first conceived in 1975 and affords a value known as the acceptor number or AN, which is a measure of solvent electrophilicity.[117] This AN has been applied by certain research groups for the measurement of Lewis acidity and typically ranges from hexane (AN = 0, weak LA) to antimony pentachloride (AN = 100, strong LA), However BCl_3 has an AN of 105.7, showing that the value of 100 is not the maximum value of Lewis acidity strength, using this classification system.

The method utilises a simple procedure whereby a 1:1 ratio of Lewis acid and triethylphospine oxide (TPO) are dissolved in deuterated benzene and the ^{31}P NMR recorded. The AN value is calculated using the following equation: $AN = (\delta_{(sample)} - 41.0) \times \{100/(86.14 - 41.0)\}$, where δ is the chemical shift in the ^{31}P NMR, the value of 41 is the chemical shift of hexane in the $^{31}P\{^1H\}$ NMR, and 86.14 the chemical shift of antimony pentachloride. We have used this method as modified, by Beckett *et al.*, to examine the Lewis acidity of Yamamoto's boron-BINOL based systems.[118]

Compound	*δ (^{31}P)[a]*	*AN[b]*
TPO	47.8	-
$B(OMe)_3$	50.2	20.4
Boron-BINOL[c]	55.2	31.5
$B(OPh)_3$	59.1	40.1
BF_3[d]	80.9	88.5
BCl_3[d]	88.7	105.7

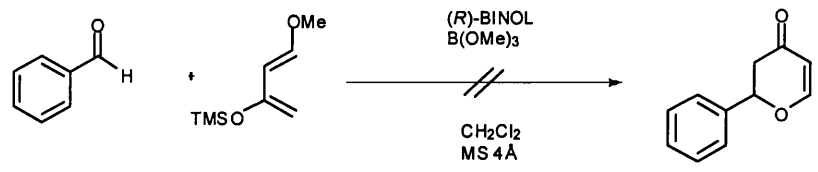
a) Spectra were recorded in C_6D_6 as 0.137M solutions at room temperature; b) The relationship $AN = (\delta_{(sample)} - 41.0) \times \{100/(86.14 - 41.0)\}$ was used to calculate AN values; c) Boron-BINOL complex formed by mixing 1 eq. $B(OMe)_3$ with 2 eq. BINOL; d) Literature values quoted.

Table 36: ^{31}P chemical shifts and acceptor numbers for boron compounds.

The table shows that trimethyl borate is a weak Lewis acid as expected and that the boron-BINOL complex possesses a greater level of Lewis acidity. This can be explained because the sp^2 carbons of the BINOL ligands are relatively electron withdrawing, hence making the boron centre more Lewis acidic when compared to the sp^3 carbons of the methoxide ligands of trimethyl borate. Interestingly triphenyl borate is slightly more acidic than the boron-BINOL complex suggesting that $B(OMe)_3$ would probably represent the best precursor for boron-BINOL formation if competing side-reactions affording racemic dihydropyridones were to be avoided.

The values obtained for boron trichloride and boron trifluoride were consistent with the literature values, thus verifying that the determination of the Lewis acidity of the boron-BINOL complex had been carried out in the correct manner.[119] This table clearly shows that although the boron-BINOL complex is Lewis acidic in nature, it is fairly weak when compared to more conventional Lewis acids such as BF_3, presumably due to back-bonding of the oxygen lone pairs of the BINOL ligand into the empty p-orbital of the boron atom.

The other point to note is that imines are stronger Lewis bases than aldehydes which may result in a stronger Lewis base - Lewis acid interaction when boron-BINOL complexes are used for catalysis. This fact may go some way to explain why the analogous hetero Diels-Alder reaction of benzaldehyde and Danishefsky's diene fails to occur under these conditions (Scheme 81).

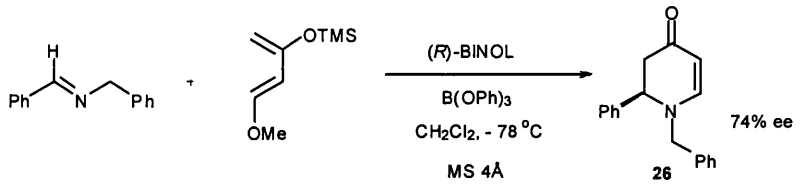


Scheme 81: Failed synthesis of aldehydes using boron-BINOL catalysts.

2.3 Yamamoto's Procedure

The original boron-BINOL mediated aza Diels-Alder reaction designed by Yamamoto is a simple procedure in which 1 eq. triphenyl borate and 1 eq. BINOL are mixed in dichloromethane with molecular sieves for one hour, followed by addition of an

aldimine and cooling to - 78 °C before the addition of Danishefsky's diene. Yamamoto claimed a yield of 75% and an ee of 82% for the formation of dihydropyridone **26** under these conditions.[24] When these exact conditions were repeated I consistently obtained a 50% yield and an ee of between 72-76%, which was slightly less than the 82% ee value claimed in the original report (Scheme 82). The enantiomeric excess of this reaction was determined using a Daicel AD chiral HPLC column, which gave baseline resolution of the two of the enantiomers and the configuration of dihydropyridone **26** confirmed as (*R*) by comparison of the negative sign of the specific rotation reported by Yamamoto for this enantiomer of $[\alpha]_D^{25}$ -8.5 (c 1, $CHCl_3$). The HPLC analysis of the dihydropyridone was carried out several times and was typically reproducible and accurate to within 2% ee.



Scheme 82: Aza Diels-Alder reaction carried under Yamamoto's conditions.

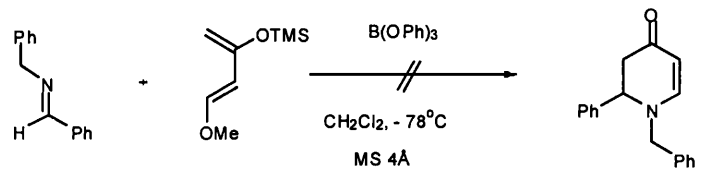
The above reaction showed some level of discrepancy with the previously reported levels of asymmetric induction and yield of the dihydropyridone product, however I was happy that the asymmetric aza Diels-Alder reaction was giving useful levels of stereocontrol and as a consequence this general reaction was chosen as the standard transformation to carry out future optimisation studies. The same aza Diels-Alder reaction at room temperature under otherwise identical conditions provided the desired pyridine product obtained in 62% yield and 30% ee, which represented a promising starting point for developing asymmetric aza Diels-Alder reactions that could operate at non-cryogenic temperatures.

2.4 Reaction rates

These initial aza Diels-Alder reactions were carried out by premixing a $B(OPh)_3$ species with BINOL prior to sequential addition of imine (at 0 °C) and Danishefsky's diene (at – 78 °C). This protocol was found to afford a reactive Lewis acid species that catalysed the aza Diels-Alder reaction in 30% ee at room temperature, and 75% ee at – 78 °C. Clearly, the dependency of stereocontrol on temperature was anticipated, however there

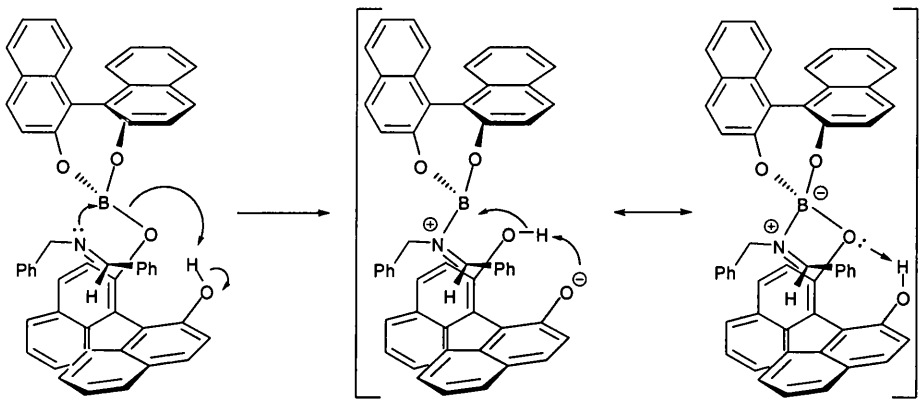
was some concern that the poor 30% ee at room temperature might be the result of unreacted $B(OPh)_3$ catalysing a background racemic reaction. Therefore, a series of reaction rate experiments were carried out comparing the reactivity of boron-BINOL complexes and $B(OPh)_3$ at – 78 °C and room temperature.

It was found that $B(OPh)_3$ alone did not catalyse the aza Diels-Alder reaction at an appreciable rate at – 78 °C, affording <10% of dihydropyridone after 5 h at – 78 °C. This compares with the situation that occurs when Yamamoto's boron-BINOL complex were employed for catalysis where the reaction proceeded to 90% conversion after 5 h at – 78 °C. Clearly, this difference in reactivity cannot be ascribed simply to the relative Lewis acidity of both complexes, since the Gutmann studies had revealed that $B(OPh)_3$ was slightly more Lewis acidic than the corresponding boron-BINOL complexes. It is therefore clear that the boron-BINOL complex must be activating the imine to nucleophilic attack in a manner that is not available to the corresponding $(PhO)_3B$-imine complex.



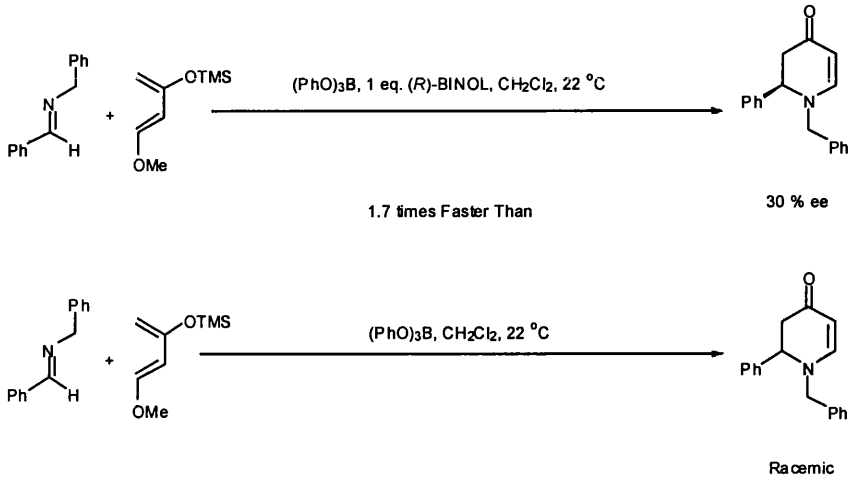
Scheme 83: Achiral background reaction proceeds at room temperature but fails at – 78 °C.

Examination of one of Yamamoto's transition states for the enantioselective reaction clearly reveals the presence of a free BINOL hydroxyl group that has the potential to act as a proton source in this reaction. We propose therefore that the increased activity observed for the boron-BINOL complex in these reactions maybe a consequence of these protons serving as Bronstead acids to help catalyse the reaction (Scheme 84).



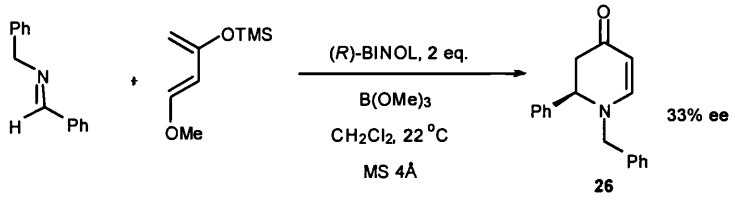
Scheme 84: Activation of imine by the boron-BINOL complex.

Comparing the reactivities of $B(OPh)_3$ and boron-BINOL as catalysts for the aza Diels-Alder reaction revealed that the enantioselective reaction at 22 °C was approximately 1.7 times faster than the corresponding achiral reaction over the first ten minutes. This determination was carried out by quenching each reaction with water, before carrying out ^1H spectroscopic analysis of each crude reaction product, which enabled the extent of reaction conversion to be determined by comparison of the integrals of resonances of starting materials and products (Scheme 85).



Scheme 85: Relative reactivities using boron-BINOL catalyst and $B(OPh)_3$.

In addition the room temperature aza Diels-Alder reaction was carried out using trimethyl borate as the boron source with two equivalents of BINOL. It was found that this boron-BINOL complex catalysed the aza Diels-Alder reaction 5.3 times quicker than the corresponding reaction using trimethyl borate. This information lead to the conclusion that the asymmetric aza Diels-Alder reaction might be improved by carrying out the reaction using trimethyl borate and 2 equivalents of BINOL. However, it was found that the use of $B(OMe)_3$ as a boron catalyst precursor only resulted in a marginal improvement in enantioselectivity at room temperature affording dihydropyridone **26** in 33% ee.



Scheme 86: Room temperature aza Diels-Alder reaction.

The results clearly demonstrated that the lower enantioselectivity observed at room temperature was not simply a consequence of unreacted $B(OMe)_3$ or $B(OPh)_3$ catalysing unwanted background racemic reaction.

2.5 NMR Investigations

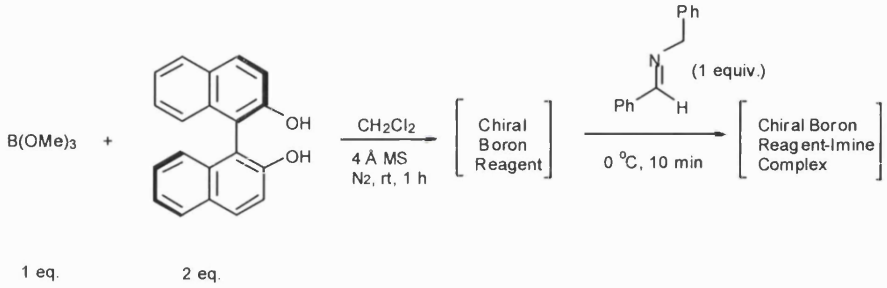
It was proposed that the most powerful method available for determining what catalytic species were present in the boron-BINOL mediated aza Diels-Alder reaction was to use NMR spectroscopic analysis. The use of ^1H NMR spectroscopy would allow for the structural determination of any intermediates formed and reveal any changes to substrates or intermediates as the reaction proceeds. ^{11}B NMR spectroscopic analysis would constitute a particularly useful technique for determining the bonding hybridisation of any boron atoms present which would help determine what type of Lewis acid – Lewis base interactions were operating between the boron and nitrogen atoms.

Therefore, I first investigated what occurred when one equivalent of benzylidenebenzylamine was mixed with one equivalent of trimethyl borate in $CDCl_3$. The purpose of this experiment was to see whether any complexation occurs between the Lewis basic imine and the weakly Lewis acidic boronate (Appendix 1.1). The ^1H NMR spectrum revealed that the resonance corresponding to the imine proton at δ8.44 had been deshielded by 0.11 ppm to δ_H 8.33 ppm possibly due to a weak interaction between the two components. The ^{11}B NMR spectrum showed no change at δ_B 19.2 ppm indicating that the boron atom remained sp^2 hybridised and that no significant nitrogen - boron interaction was occuring. These results were in agreement with the rate studies described in the previous section that indicated that $B(OMe)_3$ was a poor Lewis acid for the aza Diels-Alder reaction.

The next investigation involved mixing two equivalents of BINOL with 1 eq. trimethyl borate in $CDCl_3$ to see if Yamamoto's dimeric ate species **102** was obtained. Molecular sieves were added to the reaction to remove methanol in an attempt to drive the equilibrium of the complexation reaction to completion. The ^1H NMR spectrum surprisingly showed no new species formed, whilst the ^{11}B NMR spectrum revealed a single unchanged resonance at δ_B 19.2 ppm corresponding to $B(OMe)_3$, with no evidence of any Yamamoto's ate species having been formed. As mentioned previously

Kaufmann *et al.* have previously described the preparation of monomeric boron-BINOL species that were used for stereoselective Diels-Alder reactions, however they did not isolate or characterise this monomeric boron-BINOL species, and so it was proposed that formation of monomeric and dimeric boron-BINOL species only occurs in the presence of an imine.

In the next NMR experiment two equivalents of BINOL and one equivalent of trimethyl borate were premixed with powdered 4Å molecular sieves in dichloromethane for one hour in accordance with the standard Yamamoto procedure.[24] After this time one equivalent of benzylidenebenzylamine was added which afforded a deep yellow coloured solution that was subjected to ^{1}H and ^{11}B NMR spectroscopic analysis.



Scheme 87: Complexation experiment of boron-BINOL complex with corresponding imine.

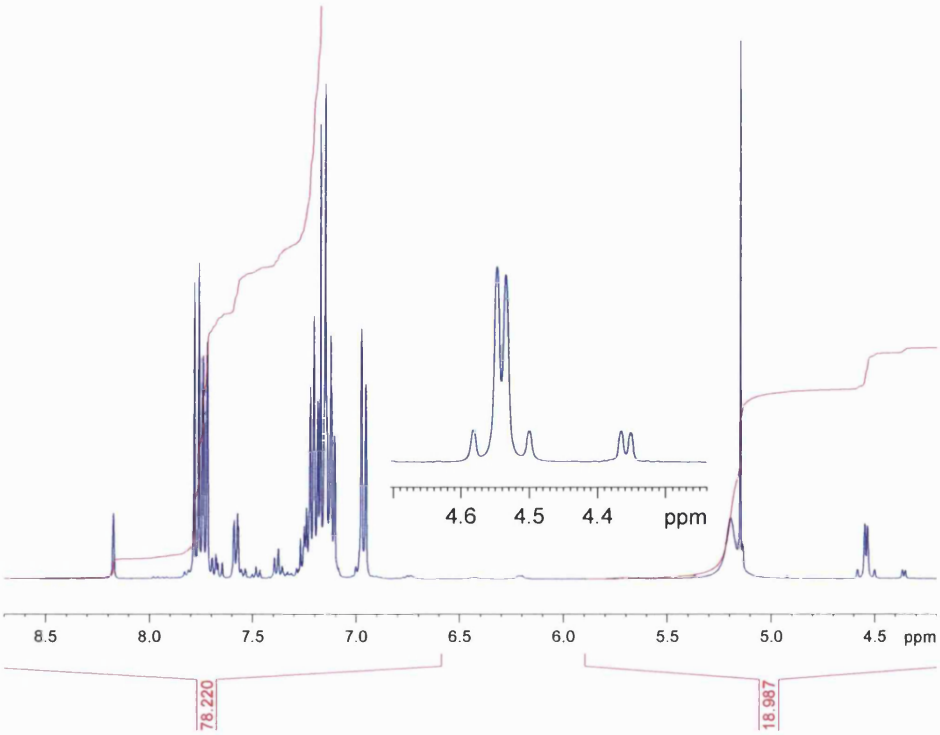


Figure 28: ^{1}H NMR spectrum of imine with a solution of BINOL-$B(OMe)_3$ showing expansion of key region.

The ^{1}H NMR spectrum of this mixture clearly showed formation of a new species. Firstly the imine proton resonance had moved from δ_H 8.44 ppm to δ_H 8.21 ppm indicating a degree of deshielding due to the new complex. In addition an AB quartet centred at δ_H 4.54 ppm had appeared that was assigned to diastereotopic benzylic protons of the imine clearly indicating the formation of a new chiral complex. This was further confirmed by the ^{11}B NMR spectrum which clearly showed a new resonance at δ_B 9.9 ppm, indicative of formation of an sp^3 boron centre. Since a previous member of our research group used non-linear effects to show that the catalyst contained two equivalents of BINOL, these results were clearly consistent with the formation of a 2:1:1 BINOL-boron-imine complex as previously suggested by Yamamoto.

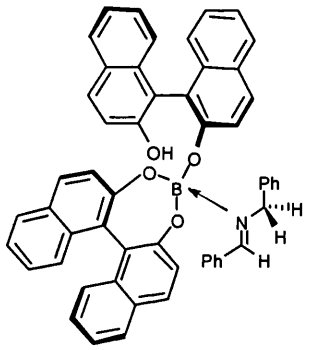
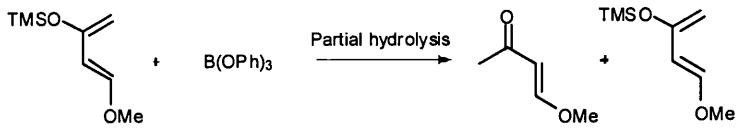


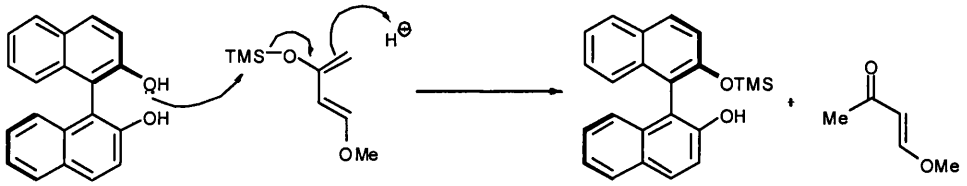
Figure 29: Possible structure of the new complex identified by NMR.

^{1}H NMR spectra of Danishefsky's diene exposed to all the reagents of the boron-BINOL mediated aza Diels-Alder reaction were then acquired. Firstly a 1:1 mixture of trimethyl borate and Danishefsky's diene was prepared which showed a mixture of unreacted diene and trimethyl borate as expected (Appendix 1.2). When Danishefsky's diene was subjected to triphenyl borate, some hydrolysis of Danishefsky's diene took place to afford its corresponding α,β-unsaturated ketone. Therefore, trimethylborate again appeared to be the reagent of choice for generating this class of catalyst. The mechanism of hydrolysis in this reaction is unclear, but it is possible that coordination of the oxygen atom of the silyl enol ester triggers silyl transfer to a phenoxy ligand, thus affording a boron enolate that is hydrolysed by adventitious phenol. This mechanistic hypothesis was tested by treating Danishefsky's diene with phenol which also resulted in the formation of partially hydrolysed diene.



Scheme 88: Hydrolysis of Danishefsky's diene in the presence of triphenyl borate.

Finally, we treated Danishefsky's diene with an equimolar amount of BINOL, which resulted in partial hydrolysis of the diene once again affording the corresponding α,β-unsaturated ketone (Appendix 1.3). In this case, silyl transfer from Danishefsky's diene to BINOL occurs to afford monosilyl-BINOL and the hydrolysed ketone (Scheme 89).



Scheme 89: BINOL mediated hydrolysis of Danishefsky's diene results in monosilyl-BINOL.

It is clear therefore that the presence of phenol or BINOL in the aza Diels-Alder reaction has the potential to hydrolyse Danishefsky's diene and affect the yield of the dihydropyridone product. However, the use of $B(OMe)_3$ with activated 4Å molecular sieves to remove methanol in the initial boron-BINOL complex formation should ensure that any methanol produced during catalyst formation would be sequested and therefore not be available to decompose Danishefsky's diene. However, its reactivity with phenolic groups does raise the possibility that a silylated imine-boron-BINOL complex could also be present in this reaction, which could potentially act as a catalytic species (Figure 30).

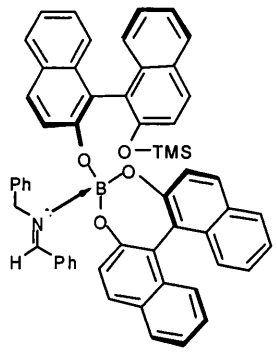
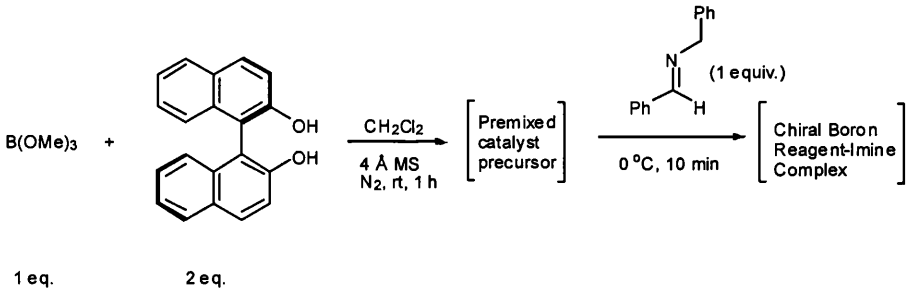


Figure 30: Possible silylated BINOL species.

2.6 Mass Spectrometric Investigations

The NMR spectroscopic investigations of the potential catalytic species had shown that the imine nitrogen atom appeared to be coordinated to a boron atom bound to a BINOL ligand, since its *N*-benzylic protons were diastereotopic, with the sp^3 character of the boron atom being evident from the ^{11}B NMR spectra. Therefore, an imine-boron-BINOL complex formed when two equivalents of BINOL, one equivalent of trimethyl borate and benzylidenebenzylamine were dissolved in dichloromethane and the resultant sample investigated using mass spectrometry.

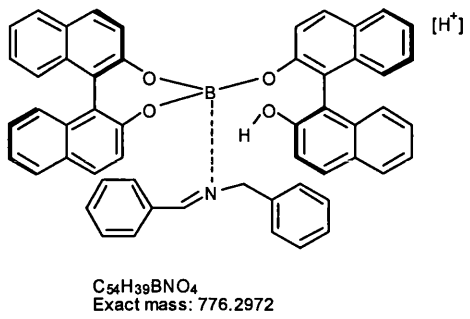


Scheme 90: Complex formed using standard Yamamoto reaction conditions.

The dichloromethane solution of the imine-boron-BINOL complex was ionised in +ESI mode, however the ionisation efficiency was weak. Adding acetonitrile to the sample improved ionisation efficiency, however only major fragment ions were observed.

Molecular ions were observed with an m\z at 971.3981, 776.3004, 391.2158 and 196.1116. Assignment of the molecular ions by accurate mass measurements (to four decimal places) allowed for accurate identification of the molecular species. The m/z of

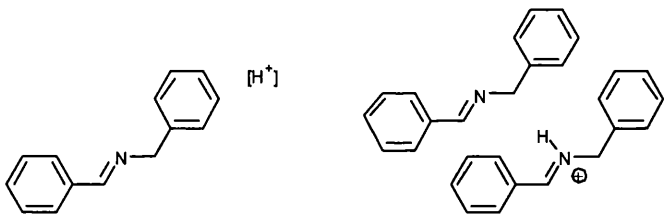
776.3004 was of most interesting fragment since this value corresponded to a boron complex containing two BINOL ligands and one equivalent of benzylidenebenzylamine (Figure 31).



$C_{54}H_{39}BNO_4$
Exact mass: 776.2972

Figure 31: Possible species for m\z 776.3004.

The fragment observed at m\z 196.1116, correlated to the iminium ion of benzylidenebenzylamine, whereas the fragment at m/z 391.2158 corresponds to the iminium salt of a benzylidenebenzylamine dimer (Figure 32).



$C_{14}H_{14}N$
Exact mass: 196.1126

$C_{28}H_{27}N_2$
Exact mass: 391.2174

Figure 32: Identified fragments of chiral boron-BINOL-imine complex.

The final observed mass ion at m/z 971.3981 can be attributed to the previously mentioned bis-BINOL-boron-imine complex with an iminium counter ion present as shown in Figure 33.

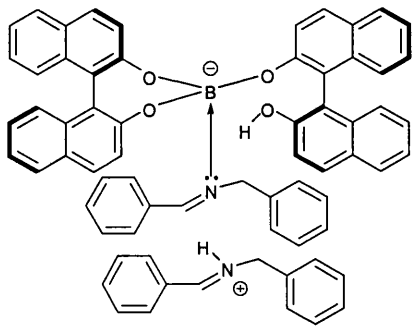
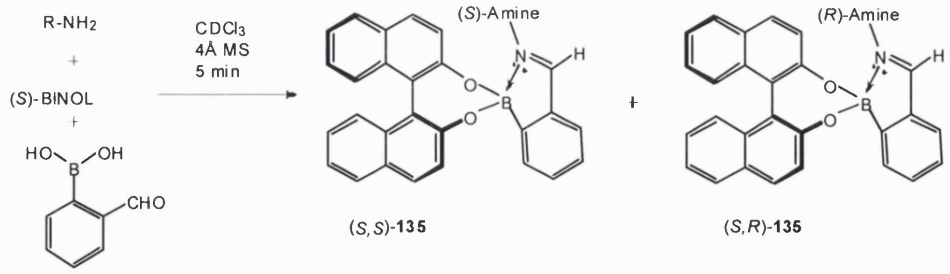


Figure 33: Probable species for m\z 971.3981.

Whether the 1:2:1 imine-BINOL-boron complex detected at 776.3004 by mass spectroscopic analysis is the reactive species responsible for asymmetric induction in these aza Diels-Alder reactions is debatable, since it may represent an artefact of the ionisation conditions employed for analysis, or a stable precursor to the enantioselective catalytic species. Nevertheless, this MS study once again demonstrates the potential intermediacy of a 1:2:1 imine-BINOL-boron complex in these reactions, thus substantiating conclusions previously drawn from ^{1}H and ^{11}B spectroscopic analysis and non-linear effect studies.

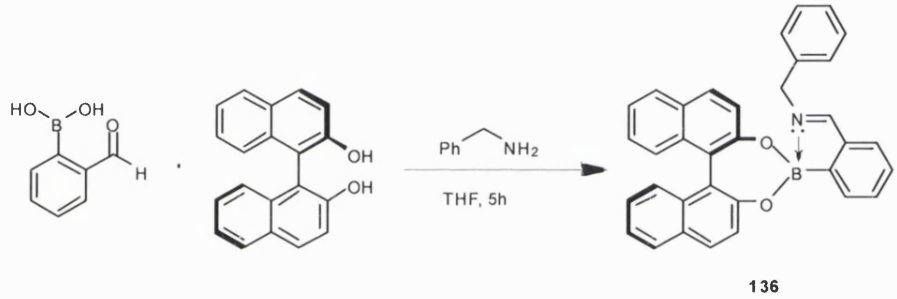
2.7 Synthesis of stable BINOL-boronates

In order to provide further evidence for the intermediacy of the 1:2:1 imine-BINOL-boron complex it was decided to investigate the reactivity of stable mimics of these potential catalytic intermediates. Previous work within the group had reported that self-assembled boron-BINOL-imine complexes such as **135** could be used for the efficient determination of the enantiomeric excess of scalemic amines.[120] The complex takes advantage of the Lewis acidic boron atom to fix the conformation of the resultant complex and allows for the successful determination of the enantiopurity of primary amines using ^{1}H NMR spectroscopy (Scheme 91).



Scheme 91: Three component derivatising agent utilising a boron-BINOL complexation reaction.

The first boronate complex synthesised involved a simple procedure in which enantiopure BINOL was mixed with 2-formyl phenylboronic acid and benzylamine in THF for five hours after which hexane was added and the desired complex precipitated from solution that was recrystalised from chloroform / hexane to afford enantiopure pure boronate **136** (Scheme 92).



Scheme 92: Formation of air stable monomeric sp^3 BINOL-boron compound.

The compound structure was confirmed by high resolution mass spectroscopy and X-ray crystallography (Figure 34), with the ^{11}B NMR spectrum displaying a resonance at δ_B 14.1 ppm inferring a partial nitrogen boron bond.

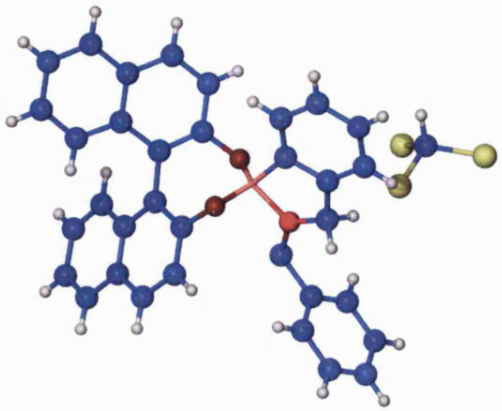


Figure 34: Crystal structure of complex (*S*)-**136** with chloroform present.

It was proposed that these complexes **136** might prove to be a useful model for the catalytic species operating in enantioselective aza Diels-Alder reactions using Yamamoto's catalyst (Figure 35)

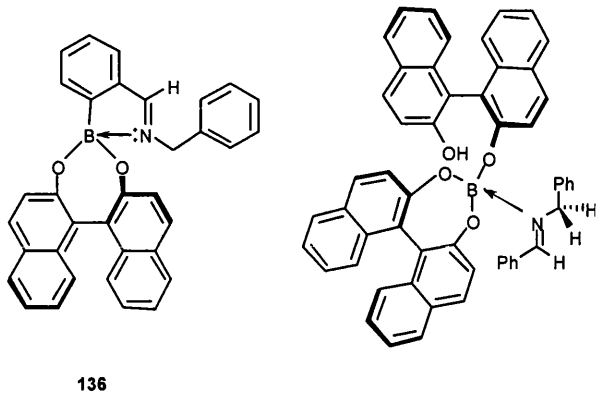
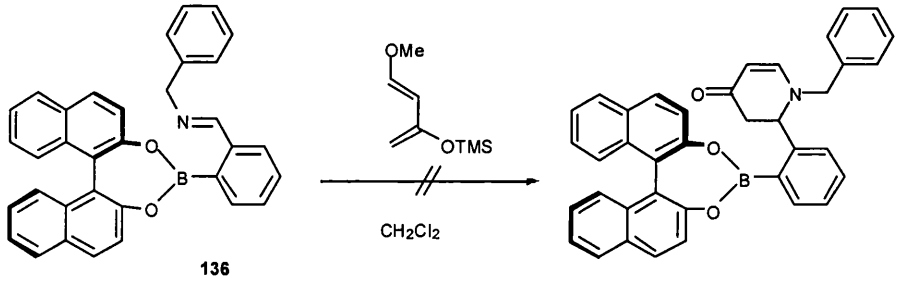


Figure 35: A comparison of our stable boronate and Yamamoto's proposed transition state.

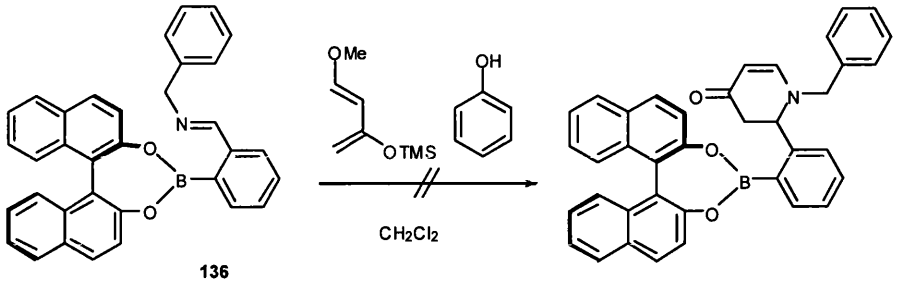
The imine-BINOL-boron complex **136** was dissolved in dichloromethane and 1.5 equivalents of Danishefsky's diene added, and the reaction stirred for 5 hours. The solvent was then removed to leave a crude reaction mixture, which ^{1}H NMR spectroscopy revealed to be unreacted boronate **136** and the hydrolysed form of Danishefsky's diene (Scheme 93).



Scheme 93: Unsuccessful reaction of boronate **136** with Danishefsky's diene.

A comparison of the structure of the stable boronate ester mimic with that of the proposed catalytic species clearly reveals some structural differences (Figure 35). One major difference between the two species is the presence of a free phenolic group containing a proton that could potentially act as a Bronsted acid to catalyse the

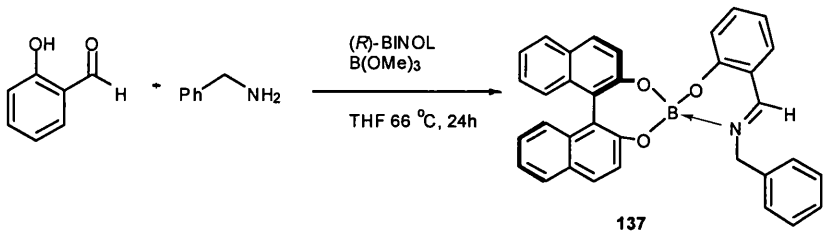
cycloaddition reaction. Therefore, the reaction of complex **136** was repeated in the presence of one equivalent of phenol, however once again no aza Diels-Alder product was formed (Scheme 94).



Scheme 94: Unsuccessful reaction of boronate **136** with Danishefsky's diene in the presence of phenol.

Another major structural difference was the fact that the stable boronate complex **136** was derived from a boronic acid fragment, whilst the proposed catalytic species contains a boronate ester fragment. Thus, the proposed catalytic species contains a boron atom bound to three oxygen atoms, whilst the stable imino-boronate complex contains a boron atom bound to only two oxygen atoms. This structural difference might have resulted in a significant difference in Lewis acidity between the two species, and thus result in the observed difference in reactivity with Danishefsky's diene.

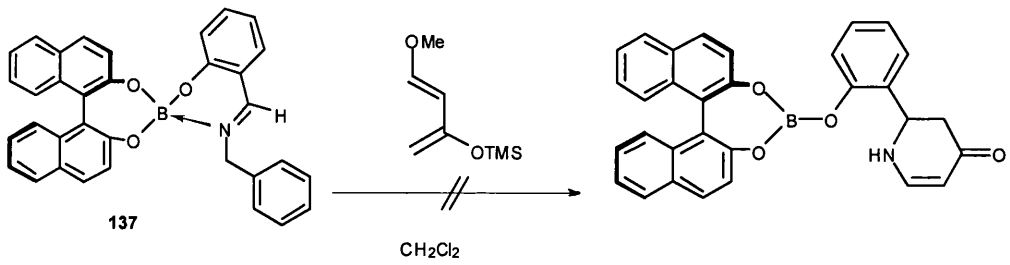
Therefore, it was decided to attempt to prepare a closer mimic of the transition state complex, which was formed from reacting, salicylic aldehyde with $B(OMe)_3$, (*R*)-BINOL and benzylamine in THF at reflux using 4Å molecular sieves to remove methanol.



Scheme 95: Formation of novel BINOL-boronate as a mimic of Yamamoto's transition state.

The resultant boronate ester species **137** was purified by recrystalisation from dichloromethane/hexane and identified by ^{1}H and ^{11}B NMR as well as by high resolution mass spectroscopic analysis. Unfortunately, it was not possible to obtain a crystal structure of this compound. In the ^{1}H NMR spectrum, the imine proton resonance appeared below 8ppm, whilst the ^{11}B NMR resonance at δ_B 5.98 ppm indicated the presence of an sp^3 boron, with a greater degree of tetrahedral character than both Yamamoto's complex (δ_B 9.9ppm) and our other stable BINOL boronate complex **136** (δ_B 14.1 ppm). Interestingly the ^{1}H NMR spectra of this boronate ester revealed the presence of approximately 20% of another structural isomer appearing, as witnessed by the presence of two AB quartets representing the diastereotopic protons of the benzylic positions. The presence of the desired boronate was further confirmed by finding a molecular ion of m/z 506.1921.

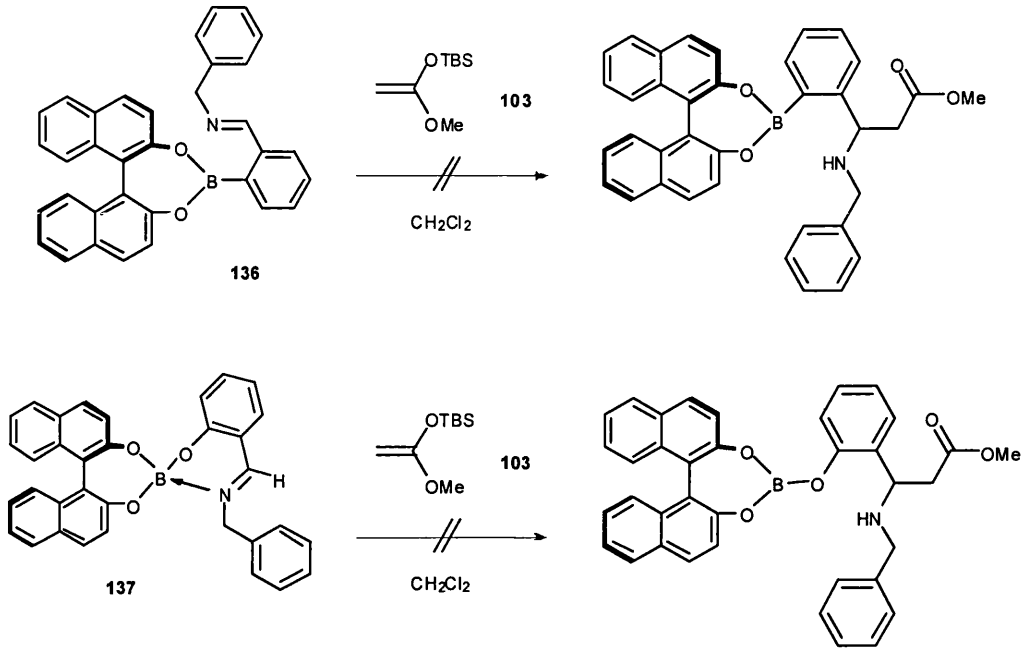
The attempts to employ this stable imino-boronate ester complex **137** in an aza Diels-Alder reaction with Danishefsky's diene proved unsuccessful, once again affording recovered starting material and hydrolysed diene as the only product (Scheme 96). Once again attempts to catalyse the aza Diels-Alder reaction in the presence of phenol as a Bronsted acid additive also proved unsuccessful, affording no evidence of any dihydropyridone having been formed.



Scheme 96: Unsuccessful reaction of boronate **137** with Danishefsky's diene.

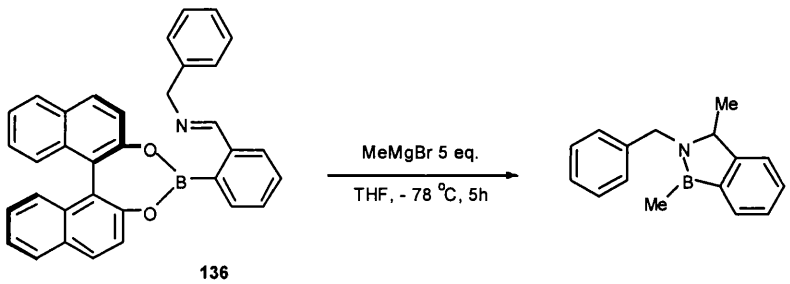
Yamamoto had also reported that boron-BINOL catalysts could be used for asymmetric Mannich type reactions,[113] therefore it was decided to screen the reactivity of our stable BINOL-boronates with silyl ketene acetal **103** in an attempt to make β-amino-ester

products. However, once again, neither of our stable boronate imino ester complexes gave any product, with starting material being recovered in both cases (Scheme 97).



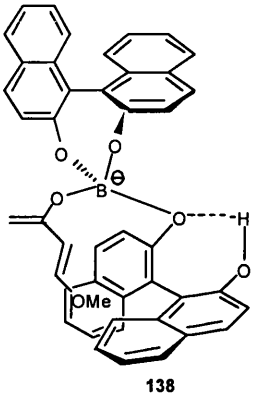
Scheme 97: Failed Mannich reactions.

It was difficult to rationalise why the stable imino-boronate ester complexes did not react with Danishefsky's diene, since they should represent good mimics of the proposed 1:2:1 imine:BINOL:boron catalyst proposed to be responsible for stereocontrol in asymmetric aza Diels-Alder reactions. Indeed, another member of the SDB/TDJ group has shown that the imine functionality of complex **136** was susceptible to nucleophilic attack by Grignard reagents in the absence of a Lewis acid, albeit affording products arising from the addition of two equivalents of nucleophile (Scheme 98).



Scheme 98: Alkylation of boronate **136** using a Grignard reagent.

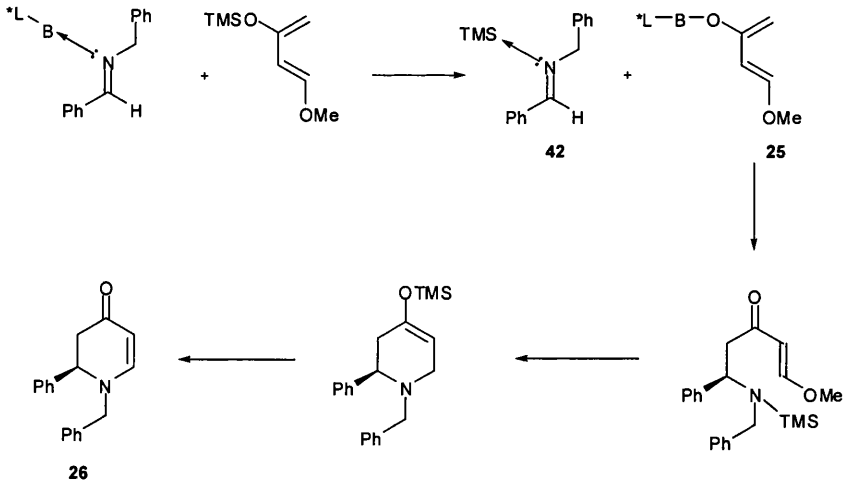
One possibility that could explain the lack of reactivity of these transition state mimics, is that the 1:2:1 Imine:BINOL:boron complex, is not the catalytic species, but acts as a 'precatalyst' reservoir that generates the true catalytic species on addition of Danishefsky's diene. Therefore, it was proposed that addition of Danishefsky's diene to the imine-BINOL-boron complex might result in transmetalation of the chiral boron complex from the nitrogen atom of the imine to the oxygen atom of Danishefsky's diene thus affording a chiral boron dienolate **138**, and a trimethylsilyl coordinated imine species (Figure 36).



138

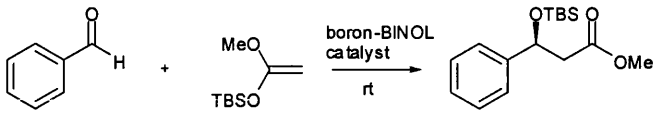
Figure 36: Chiral boron-BINOL enolate as a possible reactive species.

Subsequent reaction of these new reactive species could then result in the formation of dihydropyridone species **26** in good ee (Scheme 99).



Scheme 99: Chiral boron-enolate formation for the asymmetric aza Diels-Alder reaction.

Furthermore, research within the SDB group has shown that addition of a silyl ketene acetal to benzaldehyde in the presence of these type of boron-BINOL products results in clean formation of *O*-silylated aldol products in moderate ee, providing good evidence for silyl transfer occurring in these type of reactions (Scheme 100).



Scheme 100: Boron-BINOL catalysed aldol reaction.

Clearly, if this type of transmetalation pathway was operating in the catalytic aza Diels-Alder reactions, then it might explain why the stable imino-boronate ester complexes **136** and **137** that were prepared as catalyst mimics were unreactive under these conditions. This would be because the presence of an intramolecular nitrogen-boron bond might afford sufficient stability so that transmetalation of Danishefsky's diene does not occur, and as a consequence a boron enolate would not be generated, and as a consequence the aza Diels-Alder reaction would not proceed.

2.8 Conclusions

In this chapter we have described our investigations into the mechanism of the boron-BINOL mediated aza Diels-Alder reaction. Initially Lewis acidity tests on the boron-BINOL mediated aza Diels-Alder reaction were undertaken utilizing the Lewis acidity test developed by Gutmann *et al.*[117] Firstly it was found that trimethyl borate was only a mild Lewis acid suggesting that a competing achiral aza Diels-Alder reaction to afford racemic dihydropyridone was unlikely to be occurring when this reagent was employed as a boron precursor. Interestingly, triphenyl borate, which was previously used by Yamamoto, showed a higher level of Lewis acidity when compared to trimethyl borate, allowing us to conclude that trimethyl borate was the boron source of choice.

When trimethyl borate and BINOL were mixed in a 1:2 ratio in dichloromethane in the presence of molecular sieves, we saw an increased level in Lewis acidity when compared to trimethyl borate alone, which is ideal because this ligand accelerated

catalysis should allow for a greater rate of reaction for formation of a chiral dihydropyridone product

.

When an exact repeat of Yamamoto's original conditions for the aza Diels-Alder reaction of benzylidenebenzylamine with Danishefsky's diene at – 78 °C were followed a slightly lower enantioselectivity and yield were obtained, however the values obtained were acceptable affording dihydropyridone **26** in 72 - 76% ee in a reproducible manner. The aza Diels-Alder reaction was also carried out at room temperature under otherwise identical conditions affording the dihydropyridone **26** in a much lower 30% ee.

NMR spectroscopy was then used to examine the nature of the reactive species present in the reaction. It was found that when benzylidenebenzylamine was added to the boron-BINOL mixture then a 1:2:1 chiral boron-BINOL-Imine complex was formed whose identity was unequivocally confirmed by mass spectrometry.

Another discovery from the ^{1}H NMR spectroscopic analysis was that Danishefsky's diene was hydrolysed in the presence of BINOL, to afford an α-β-unsaturated ketone and TMS-BINOL respectively. This observation clearly has implications for the yield of dihydropyridones in these reactions, whilst it cannot be discounted that TMS-BINOL might play an important role in facilitating these asymmetric transformations.

Finally, we prepared novel BINOL-boronates as plausible transition state mimics of the catalytic boron-BINOL-imine complex. Unfortunately they did not react with Danishefsky's diene in the way they were intended, and as a consequence further work is currently underway within the TDJ/SDB group to probe the potential intermediacy of chiral boron-enolate complexes in these asymmetric aza Diels-Alder reactions.

3 Results and Discussion 2: Optimisations and new strategies for the Boron-BINOL mediated aza Diels-Alder reaction

3.1 Introduction

In the previous chapter we investigated the boron-BINOL mediated aza Diels-Alder reaction, which was first conceived by Yamamoto and colleagues.[23] This method is currently one of the best approaches to synthesising chiral pyridones when the range of methodology avaliable is considered.

The key advantages of the boron-BINOL method are that the synthesis is very practical; the reagents are commercially available with BINOL costing less than £1.00 per gram; the level of chiral induction is generally high, usually between 70 – 90 % ee for a range of imine substrates at – 78 °C.

The current boron-BINOL method does have disadvantages however, specifically the fact that stoichiometric quantities of BINOL and trimethyl borate are required, which can result in difficulties during purification of dihydropyridone products via chromatography due to the presence of large amounts of BINOL. The other issue is temperature since these type of boron-BINOL catalysed aza Diels-Alder reactions are normally carried out at – 78 °C, which is non-optimal for reaction scale up.

3.1.1 Aims and objectives

In the previous chapter we examined a number of features of the boron-BINOL mediated asymmetric aza Diels-Alder reaction. From considering these experiments, the next aim was to design a boron-BINOL based asymmetric aza Diels-Alder methodology which improved on the original catalytic system developed by Yamamoto *et al.* The main target of this stage of the project were to devise conditions that reproducibly afforded higher levels of enantiopurity for a range of aza Diels-Alder substrates in good yield. Another goal was to develop reaction conditions that would allow for respectable levels of enantiopurity to be obtained at room temperature, since

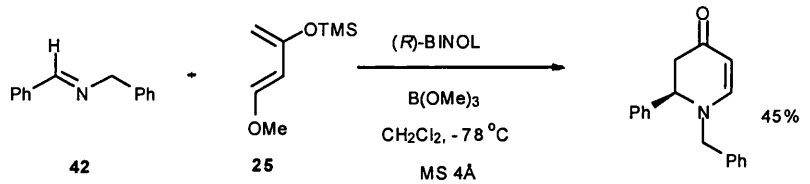
an efficient asymmetric methodology for the synthesis of chiral nitrogen heterocycles at non-cryogenic temperature would be welcomed by the wider synthetic community. Finally, I wanted to determine conditions that would enable boron-BINOL complexes to function at low catalytic loadings, thus avoiding the purification difficulties associated with the use of stoichiometric amounts of BINOL.

3.2 Optimising the boron-BINOL aza Diels-Alder reaction

The boron-BINOL mediated aza Diels-Alder reaction designed by Yamamoto is a simple procedure in which 1 eq. triphenyl borate and 1 eq. BINOL are mixed in dichloromethane with molecular sieves for one hour, addition of an aldimine, followed by cooling to - 78 °C and addition Danishefsky's diene. These reaction conditions were originally reported to afford chiral pyridone products in moderate to good yields (75%) and reasonable enantioselectivities (82%).[24] As described in the previous chapter I initially obtained a slightly lower level of asymmetric induction of 72-76% ee and 50% yield for the standard aza Diels-Alder reaction between imine and Danishefsky's diene **25**, and as a consequence a series of optimisation studies were carried out.

3.2.1 Enhancing the yield

The first area investigated was to improve the yield of the asymmetric aza Diels-Alder reaction. Yamamoto reported that the BINOL-boron reagent, created from a 1:1 mixture of trimethyl borate and (*R*)-BINOL gave a modest yield of 45% when benzylidenebenzylamine **42** and Danishefsky's diene were used as reactants in equimolar quantities (Scheme 101).[24]



42 25

Scheme 101: Yamamoto's aza Diels-Alder reaction using equimolar amounts of reagents and substrates.

Since it was now known that the active catalyst contained more than one equivalent of BINOL we initially attempted to increase the yield of dihydropyridone product by increasing the number of equivalents of BINOL used for catalyst formation. Carrying

out the same aza Diels-Alder reaction as Yamamoto using identical conditions and one equivalent of (*R*)-BINOL afforded a 48% yield of dihydropyridone. Next, a series of experiments were carried out using two, three and four equivalents of BINOL for catalyst formation. Each crude reaction was analysed by ^{1}H NMR spectroscopy in $CDCl_3$ in the presence of a known quantity of 2,5-dimethyl furan as an internal reference standard. Analysis of the reaction integrals of respective peaks corresponding to the imine, Danishefsky's diene, dihydropyridone and the known amount of 2,5-dimethylfuran enabled accurate determination of the yield/conversion of these reactions. The results are described in the Table 37 below:

BINOL equiv.	*Diene equiv.*	*Imine equiv.*	*Yield, %*
1	1	1	**48**
2	1	1	**70**
3	1	1	**60**
4	1	1	**60**

Table 37: Yield when varying number of BINOL equivalents.

These results showed that increasing the number of BINOL ligands from one to two equivalents gave a considerable increase in the yield, however, when three or four equivalents of BINOL were used the yield of dihydropyridone product obtained was significantly lower. It is proposed that the loss in yield is probably a consequence of the free hydroxyl group of BINOL competitively hydrolysing the Danishefsky's diene, thus lowering the yield of the aza Diels-Alder reaction.

In the next series of reactions the number of equivalents of Danishefsky's diene in the aza Diels-Alder reaction was varied. It had been shown by NMR experiments that Danishefsky's diene was readily hydrolysed by BINOL, so it was expected that addition of more than one equivalent of diene might result in an increase in the yield of dihydropyridone **26** (Table 38).

BINOL equiv.	*Diene equiv.*	*Imine equiv.*	*Yield, %*
2	**1**	1	**70**
2	**2**	1	**74**
2	**4**	1	**75**

Table 38: Yield of dihydropyridone obtaibed when varying number of Danishefsky's diene equivalents.

The table shows that using two equivalents of Danishefsky's diene resulted in a slightly greater 74% yield of dihydropyridone product, however adding four equivalents of this relatively expensive diene did not afford any further benefit.

The final yield optimisation experiment involved changing the number of equivalents of benzylidenebenzylamine employed in the aza Diels-Alder reaction which revealed that the use of one equivalent of imine **42** was optimal for this reaction (Table 39). Therefore, adding two equivalents of imine drastically reduced the yield of dihydropyridone whilst using four equivalents resulted in no dihydropyridone product being produced.

BINOL equiv.	*Diene equiv.*	*Imine equiv.*	*Yield, %*
2	1	1	**70**
2	1	2	**20**
2	1	4	**Failed**

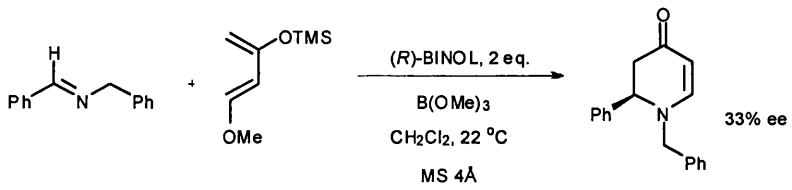
Table 39: Yield of dihydropyridone obtained when varying number of imine equivalents.

This failure to observe any dihydropyridone whatsoever was somewhat surprising, however it is possible that the presence of extra equivalents of imine results in essentially irreversible coordination of the imine lone-pairs to the boron catalyst. This offers the intriguing possibility that the trans-enolisation *N-O* boron transfer mechanism discussed in the previous chapter may be suppressed, and as a consequence no aza Diels-Alder reaction occurs.

3.2.2 Aza Diels-Alder reaction at Varied Temperature

In previous work carried out by Yamamoto there was no report of boron-BINOL catalysed aza Diels-Alder reactions being carried out at temperatures above – 78 °C.[23,24,113] It was decided that it would be of great interest to examine the level of enantioselectivity achieved at ambient temperatures, given that most large scale industrial processes prefer to carry out reactions at room temperature due to cost and practicality considerations.

As described, we initially carried out the aza Diels-Alder reaction using two equivalents of BINOL and one equivalent of trimethyl borate, using benzylidenebenzylamine and Danishefsky's diene as substrates (Scheme 102).



Scheme 102: Room temperature aza Diels-Alder reaction.

This reaction was carried out under nitrogen and stirred at room temperature for five hours yielding the desired product in 62% yield and 33% ee. The fact that any degree of enantioselectivity was observed was encouraging, given the potential for optimisation that might lead to a more stereoselective reaction at room temperature.

We also carried out the reaction using five equivalents of BINOL to see if the enantioselectivity could be increased which gave dihydropyridone in a much reduced 35% yield, whilst the enantiomeric excess was only slightly increased to 37% ee. The standard aza Diels-Alder reaction was also carried out at 0 °C, with the enantiomeric excess increasing to 47% ee, whilst at reflux the reaction afforded racemic product (Table 40).

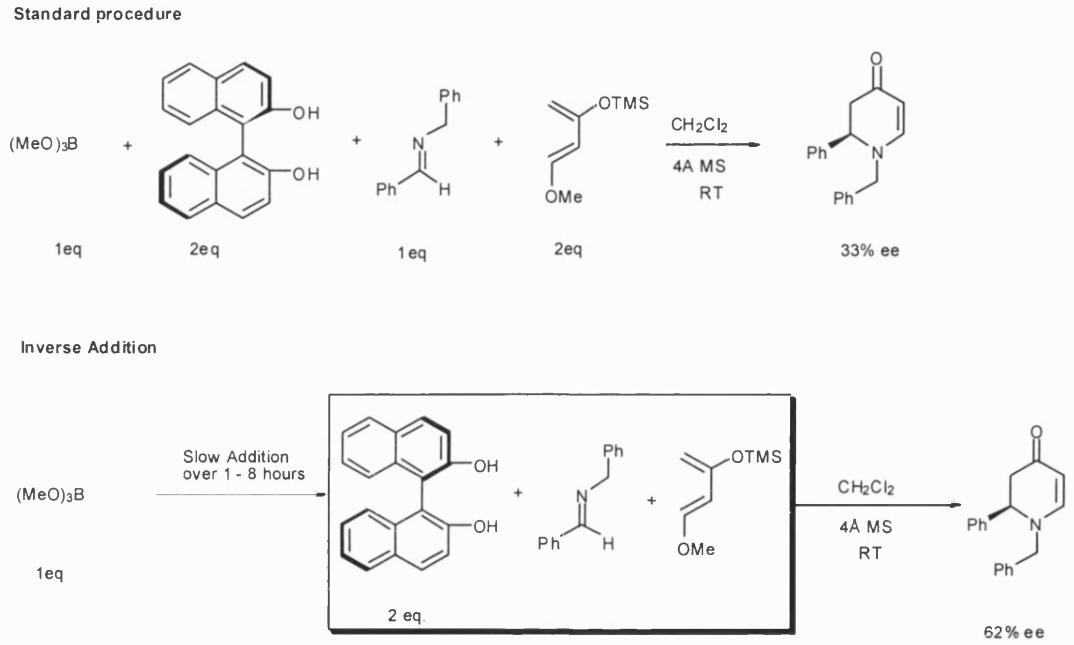
Temperature, °C	*BINOL equiv*	*Yield, %*	*ee, %*
- 78	2	70	74
0	2	63	47
22	2	62	33
22	5	35	37
40	2	73	rac

Table 40: Change in enantiomeric excess of dihydropyridone at different temperatures.

3.2.3 Inverse additions

In an attempt to limit formation of racemic dihydropyridone arising from the achiral background reaction it was decided to add the trimethyl borate slowly to the other

reagents using a syringe pump. It was proposed that this would allow the imine and diene to mix together with no reaction taking place. Then as the trimethyl borate was added the boron atom would undergo rapid ligand exchange with the BINOL to generate a chiral boron complex that would catalyse the chiral aza Diels-Alder reaction. This would minimise the amount of excess trimethyl borate present at any one time, thus suppressing the achiral background reaction and ensuring that the enantiomeric excess of the pyridone would be maximised (Scheme 103).



Scheme 103: A comparison of the standard reaction and the inverse addition reaction at room temperature.

A range of experiments were therefore carried out in which the addition time of the trimethyl borate to the other reactants was varied. The table below shows the key results obtained:

Addition time	*Temperature °C*	*Yield*	*ee,%*
0.5 mins	22	60	37
25 mins	22	62	50
5 hours	22	55	**62**
5 hours	0	67	58
5 hours	- 78	67	68
8.5 Hours	22	44	55

Table 41: Aza Diels-Alder reaction using inverse addition method.

These results clearly showed that slow addition of trimethyl borate gave rise to a significant increase in enantiomeric excess when compared to the standard room temperature reaction conditions that normally afford the dihydropyridone in 33% ee, with the inverse addition method over 5 hours affording the desired pyridone in an ee of 62%. When the inverse reaction was carried out at 0 °C there is an approximate increase of 10 % ee. when compared to the standard preparation at 0 °C. The table also shows that using the inverse addition method at 0 °C gives a slightly lower enantiomeric excess than when the reaction is carried out at room temperature (58% ee compared with 62% ee). This is probably due to the fact that the achiral background reaction, which is catalysed solely by the trimethyl borate, is limited at lower temperatures and hence the inverse addition strategy does not afford a significant advantage at lower temperature. The enantiomeric excess at – 78 °C is unfortunately not improved upon using the inverse addition procedure affording dihydropyridone in 68% ee. This can also be attributed to the achiral background reaction having no significant effect at these reduced temperatures. The yields of the inverse addition reaction were generally similar to the yields obtained when the reaction was carried out using the standard Yamamoto protocol.

3.3 Additives and the Aza Diels-Alder reaction

The next stage of the investigation involved using a boron-BINOL catalysed aza Diels-Alder catalyst involving the addition of various additives in an attempt to improve the enantioselectivity of the reaction. This additive approach has been used previously to tune the stereoselectivity of other reactions including methodology developed by Kobayashi who used the ligand NMI (*N*-methyl imidazole) to increase the enantioselectivity of aza Diels-Alder reactions up to 93% ee (Figure 37).[54]

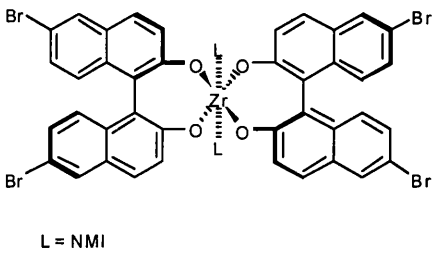
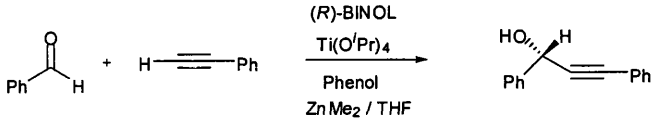


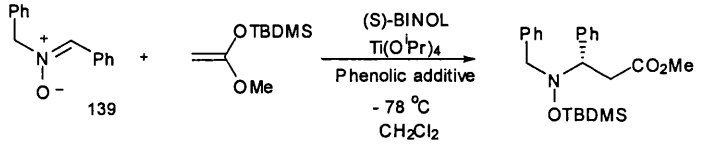
Figure 37: Additives used by Kobayashi in his BINOL-zirconium Lewis acid.

Chan *et al.* have shown how the use of phenolic additives in the asymmetric alkynylation of benzaldehyde resulted in an increase in enantioselectivity and yield.[121] They found that when phenol was added to a titanium-BINOL Lewis acid system, the enantioselectivity increased from 90% ee to 96% ee. They also noticed an increase in yield from 78% to 84%. Other phenolic additives had similar positive effects including 2-naphthol and 4-bromo-phenol (Scheme 104).



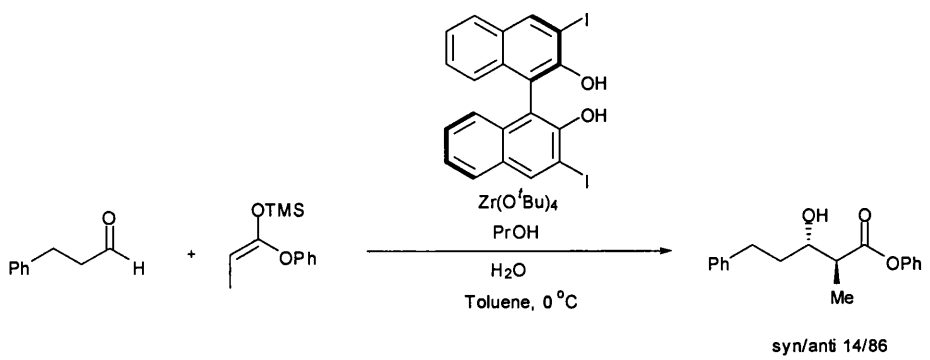
Scheme 104: Asymmetric alkynylation using phenolic additives.

Murahashi *et al.* showed how the use of phenolic additives can drastically increase the enantioselectivity of the asymmetric silyl ketene acetal addition to nitrone **139** (Scheme 105).[122] The addition of phenol resulted in an increase of enantioselectivity from 18% ee to 34% ee. This was further increased by using catechol, which afforded a 73% ee whilst 4-*tert*-butylcatechol gave a further improvement to 92% ee. Both catechol type additives resulted in a reversal in the sense of asymmetric induction, which unfortunately was not explained by the author (Scheme 105).



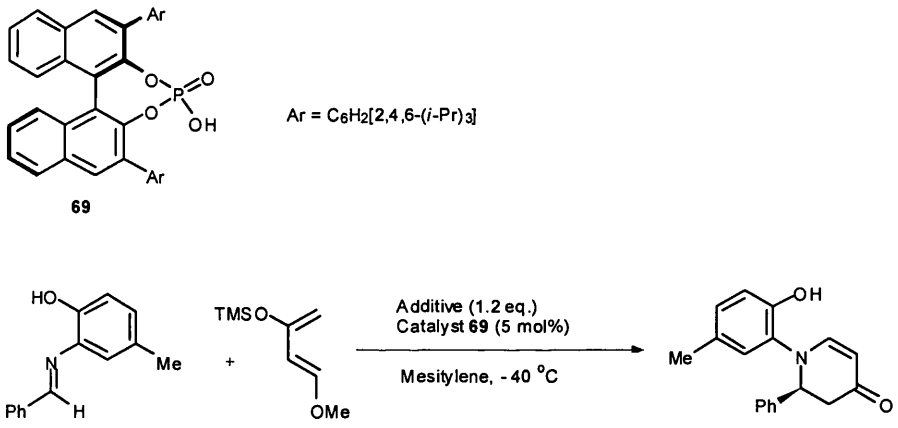
Scheme 105: Asymmetric addition of silyl ketene acetal to nitrones using phenolic additives.

Kobayashi *et al.* showed how adding water to asymmetric aldol reactions afforded the desired aldol product in a greatly improved yield and increased enantioselectivity.[123] They found the optimal conditions involved addition of 20 mol% water, which afforded the desired product in 61% yield, compared with 31% with no water. The enantioselectivity was increased from 85% ee to 89% ee, however the use of 40 mol% water resulted in no product formation (Scheme 106).



Scheme 106: Asymmetric Mukiyama aldol reaction using water as an effective additive.

Another example whereby an additive has a positive effect on enantioselectivity was shown in a recent publication by Akiyama *et al.* They employed a chiral Bronsted acid to catalyse an aza Diels-Alder reaction between Danishefsky's diene and aldimine **69** (Scheme 107).[65]



Scheme 107: BINOL based phosphoric acid catalysed asymmetric aza Diels-Alder reaction.

Additive	*Yield, %*	*ee, %*
None	*29*	*34*
MeOH	*97*	*46*
BnOH	*81*	*60*
CF_3CH_2OH	*88*	*41*
$PhCO_2H$	***85***	***63***
CH_3CO_2H	*78*	*67*
$PhSO_3H$	*87*	*15*

Table 42: The effect of protic additives on the chiral Lewis acid catalysed aza Diels-Alder reaction.

They employed a series of additives which ranged from alcohols such as methanol and benzyl alcohol to acids like acetic acid and phenyl sulfonic acid. The levels of enantioselectivity could be effectively doubled by simple use of these additives, however, the author offered no explanation for the increases. It should be noted that this particular example of employing additives to increase enantioselective induction was published after the work described in the next section of this thesis, was carried out.

3.3.1 Chiral Additives

In the past the SDB research group has shown that dynamic ligand exchange occurs at the boron centre of boron-BINOL catalytic systems since non-linear effects are known to operate in this system.[26] With this knowledge it was decided to investigate what effect the addition of stoichiometric amounts of various chiral alcohol additives to the aza Diels-Alder reaction would have on the enantioselectivity of the reaction. It was proposed that one of the hydroxyl groups of a BINOL moiety of the catalytic complex might be replaced by a chiral alcohol ligand, which in turn might have a positive influence on the asymmetric induction of the boron-BINOL mediated aza Diels-Alder reaction. The figure below shows the type of tuneable complexes that might be formed when a chiral alcohol is added to the aza Diels-Alder reaction (Figure 38).

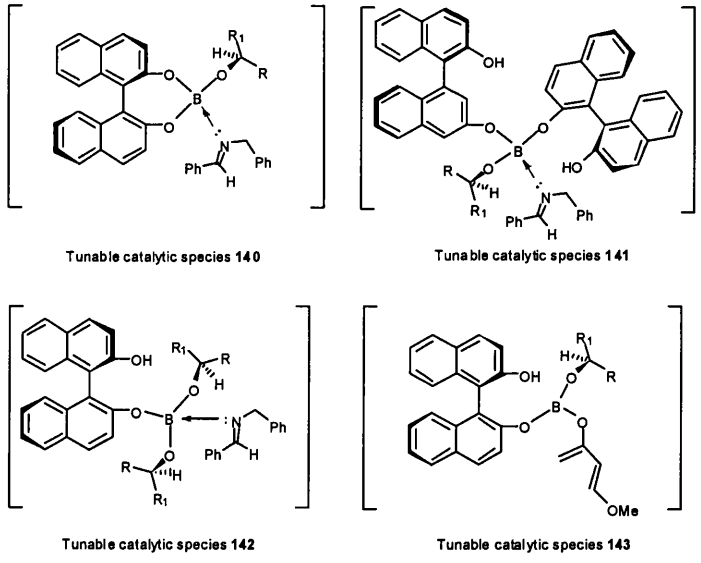
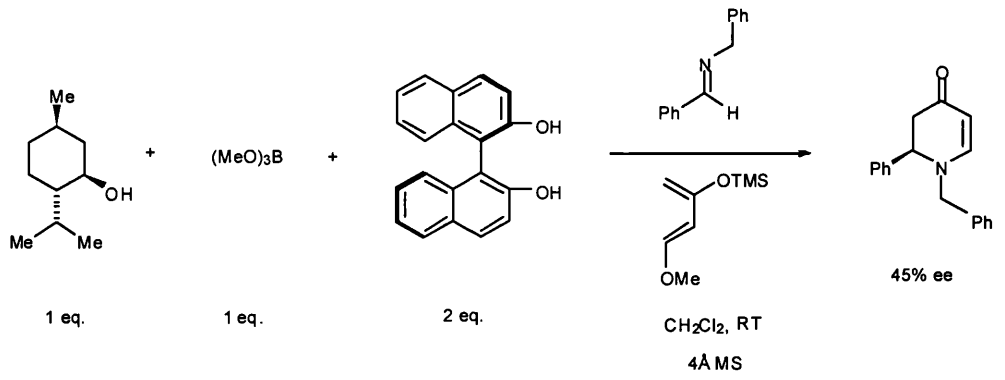


Figure 38: Chiral alcohols used as additives to tune enantioselectivity of aza Diels-Alder reaction.

The first modified catalytic species **140** could involve the complete replacement of a BINOL ligand with another chiral alcohol. Alternatively, a modified catalytic species

141 could occur that was comprised of two equivalents of BINOL, and one equivalent of chiral alcohol additive, or one equivalent of BINOL and two equivalents of chiral alcohol **142**. Finally, it is possible that transmetalation to afford a boron enolate containing a BINOL ligand and chiral alcohol additive might occur as shown for species **143**. Therefore, given the wide range of chiral alcohols that are commercially available, this additive approach might allow the steric and electronic properties of the catalytic species to be optimised in a combinatorial manner.

The first chiral alcohol employed as an additive was menthol, with the aza Diels-Alder reaction being carried out by simply adding one equivalent of alcohol to a standard room temperature reaction using two equivalents of (*R*)-BINOL and one equivalent of trimethyl borate. These three reagents were premixed in methylene chloride for a period of one hour with 4Å molecular sieves, before benzylidenebenzylamine was added, followed by addition of Danishefsky's diene at room temperature. The reaction proceeded as expected yielding the desired pyridone with an enantioselective excess of 45% ee, which represented a promising 12% increase on the enantioselectivity obtained when no menthol was added (Scheme 108).



Scheme 108: Pyridone formation reaction enhanced using menthol as a chiral additive.

Encouraged by these results it was decided to carry out the same aza Diels-Alder reaction using the opposite enantiomer of BINOL. It was expected that the enantiomeric excess produced would be lower than the reaction using (*R*)-BINOL as the (*S*)-BINOL and the enantiomer of menthol would result in mis-matched stereocontrol and hence reduce the facial selectivity of the aza Diels-Alder reaction. The reaction using (*S*)-

BINOL did indeed give a lower ee of 27%, which is a lower value of selectivity than the 33% ee obtained when the aza Diels-Alder reaction was carried out with no additive.

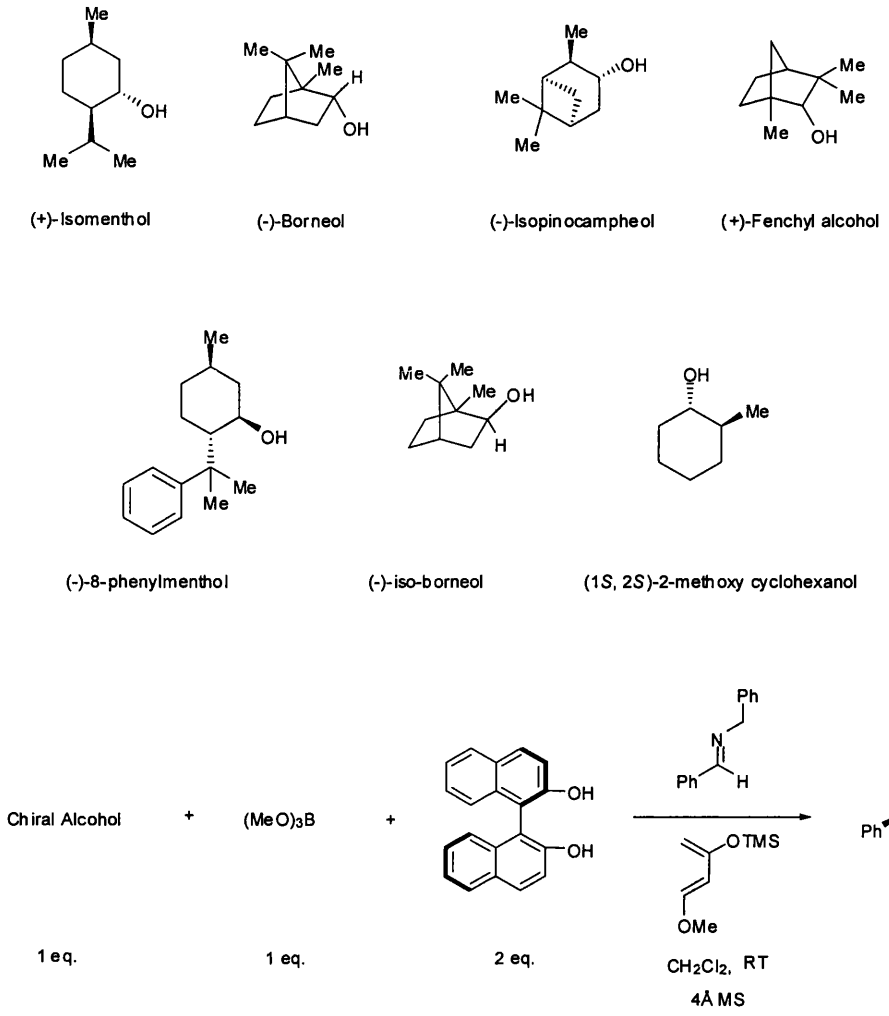
To examine the individual effect of the menthol additive alone we repeated the aza Diels-Alder reaction in the absence of BINOL, which led to the formation of a racemic pyridone product. This complete lack of stereocontrol suggests that menthol does not coordinate to the boron in the absence of BINOL, resulting in racemic pyridone formation to be exclusively catalysed by trimethyl borate.

Menthol equiv.	*BINOL equiv. (R/S)*	*Temperature, °C*	*ee, %*
0	1 (*R*)	22	33
1	**2 (*R*)**	**22**	**45**
1	2 (*S*)	22	27
2	0	22	2
1	1 (*R*)	-78	71

Table 43: Boron-BINOL catalysed aza Diels-Alder reaction using the chiral alcohol menthol as an additive.

Finally, we carried out the same boron-BINOL catalysed aza Diels-Alder reaction at - 78 °C using menthol as an additive to afford the dihydropyridone adduct in 71% ee. Therefore, the use of menthol as an additive did not significantly increase the enantioselectivity of the aza Diels-Alder reaction at – 78 °C (Table 43).

Given the availability of a range of terpene derived chiral alcohols we decided to screen five further terpenols to examine their effect on the enantioselectivity in the boron-BINOL mediated aza Diels-Alder reaction at room temperature. In addition we also screened two other commercially available alcohols, which were (-)-8-phenylmenthol and (1*S*, 2*S*)-2-methoxy cyclohexanol that were available in the laboratory (Scheme 109).



Scheme 109: A selection of chiral alcohols that were screened in the boron-BINOL mediated aza Diels-Alder reaction at room temperature.

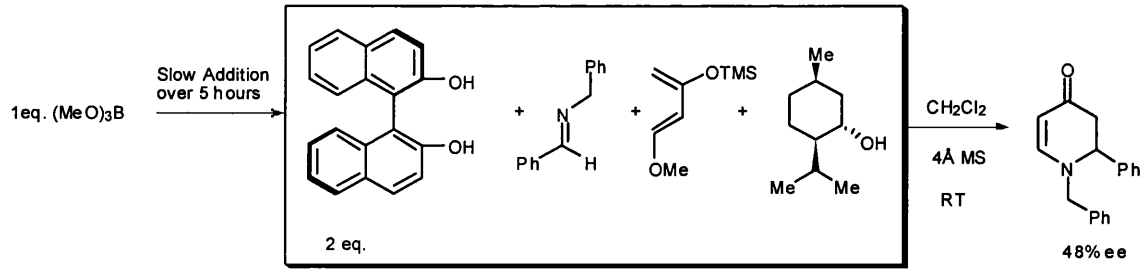
The same reaction conditions were used for which menthol had given a 12% increase in enantioselectivity. It was found that the best result arose from using enantiopure (+)-*iso*-menthol and (*R*)-BINOL, which gave dihydropyridone in 52% ee, which is an increase of 19% over the corresponding non-additive reaction. The other alcohols all gave enantioselectivities lower than when using menthol, however higher levels of asymmetric induction were observed in all cases when compared the 33% ee obtained for the aza Diels-Alder reaction when no chiral additives were employed (Table 44).

Chiral additive	*Temperature, °C*	*Yield, %*	*ee, %*
None	22	62	33
Menthol	22	60	45
***Iso*-menthol**	**22**	**61**	**52**
Borneol	22	58	44
Iso-borneol	22	60	41
Fenchyl alcohol	22	57	41
Iso-pinocampheol	22	55	38
8-phenylmenthol	22	52	35
(1*S*, 2*S*)-2-methoxy-cyclohexanol	22	60	43

Reaction conditions: BINOL (2 eq.), $B(OMe)_3$ and chiral additive mixed in dichloromethane with 4Å molecular sieves for 1h, after which benzylidenebenzylamine (1 eq.) was added followed by Danishefsky's diene.

Table 44: Results from the boron-BINOL mediated aza Diels-Alder reaction using chiral additives.

It was then decided to see whether the improved enantioselectivities observed for the inverse addition approach and the chiral additive strategy could be combined to afford a dihydropyridone in high ee at room temperature. Therefore, trimethylborate was added dropwise, over a period of 5 hours to a solution of benzylidenebenzylamine and Danishefsky's diene, (*R*)-BINOL (2 eq.) and *iso*-menthol (1 eq.) in dichloromethane which led to the formation of the desired pyridone in 64% yield, with enantioselectivity of 48% ee. Unfortunately this value turned out to be lower than if both methods were carried out separately, which maybe a consequence of the fact that trimethyl borate, BINOL and *iso*-menthol need to be premixed together at the start of the reaction for the additive strategy to afford improved levels of stereocontrol (Scheme 110).

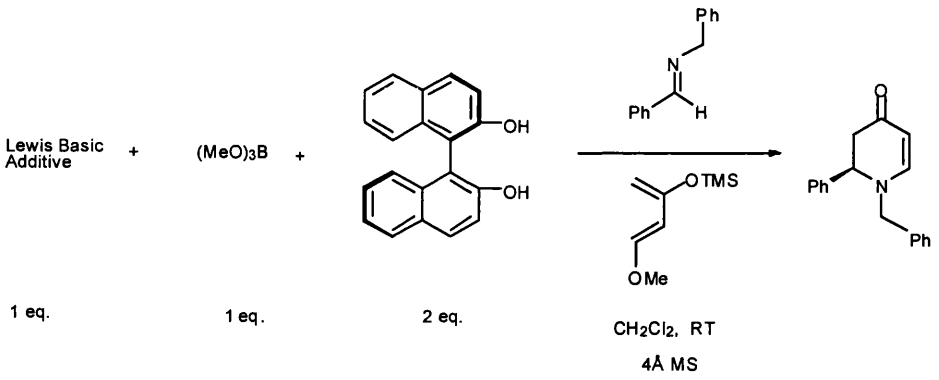


Scheme 110: Inverse addition using enantiopure *iso*-menthol as a chiral additive.

3.3.2 Boron-BINOL mediated aza Diels-Alder reaction with achiral additives

In the previous section the use of chiral alcohols as additives for the boron-BINOL mediated aza Diels-Alder reaction was investigated and it was shown that certain chiral alcohols principally menthol and *iso*-menthol gave an increase in enantioselectivity. This increase was attributed to the alcohol additive coordinating to the boron centre and hence altering the geometry of the substrate bound to the boron-BINOL complex, thus improves the resulting level of asymmetric induction.

Given the literature precedent described, it was proposed that the influence that the chiral additive had on these asymmetric aza Diels-Alder reactions might not be entirely due to the stereogenic centres of the additive and for this reason it was deemed necessary to investigate other non-chiral Lewis basic additives in this reaction. The Lewis basic additives chosen were alcohols, amines, a sulphide, a sulfoxide and a phosphine oxide that were available in the laboratory (Figure 39).



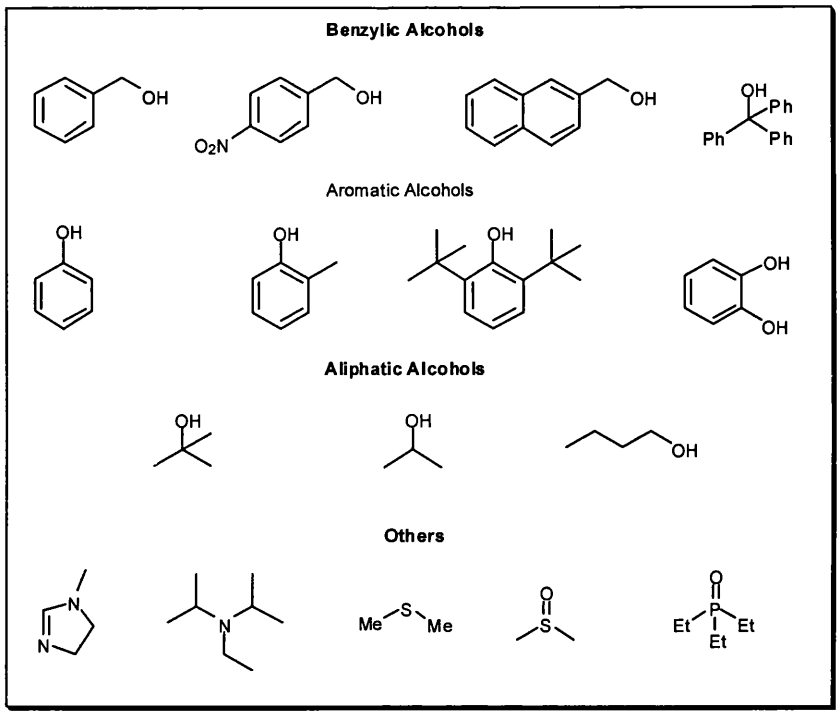


Figure 39: Aza Diels-Alder reaction using a range of non-chiral additives.

The reaction protocol carried out was identical to the conditions used when chiral alcohols were used as additives. We initially added benzyl alcohol, which gave a significant increase in enantioselectivity at room temperature (52% ee.). This result matched the same level of selectivity achieved when 1eq. of *iso*-menthol was used, which meant that the use of a chiral alcohol as additives was unnecessary. Next we used the more electron withdrawing 4-nitrobenzyl alcohol which also gave the same value of 52% ee. 2-Naphthylmethyl alcohol was also screened, reasoning that a naphthyl group would add greater steric demand to the catalyst when compared to the benzyl alcohols, however only a 42% ee for dihydropyridone **26** was obtained.

Phenol and *o*-cresol were then used as additives to examine their effect on enantioselectivity and it was found that phenol gave 48% ee while *o*-cresol gave a 44% ee. The sterically hindered 2,6-ditertbutylphenol also gave similar levels of enantioselectivity, affording dihydropyridone in 45% ee. Catechol gave a much lower level of enantioselectivity (31% ee.), potentially because of bidentate binding to the boron centre, which in turn would not allow binding of a second BINOL ligand and therefore reduce the asymmetric induction of the catalyst (Table 45).

Additive	*Temperature, °C*	*ee, %*
Benzyl alcohol	**22**	**52**
4-Nitrobenzyl alcohol	**22**	**52**
2-Naphthylmethyl alcohol	22	44
Triphenylmethanol	22	46
Phenol	22	48
o-Cresol	22	44
2,6-di-*tert*-butylphenol	22	45
Catechol	22	31
t-Butanol	22	40
***i*-Propylalcohol**	**22**	**50**
***n*-Butanol**	**22**	**50**
*N-M*ethylimidazole	22	34
Diisopropylethylamine	22	30
Dimethylsulfide	22	42
Dimethylsulfoxide	22	38
Triethylphosphine oxide	22	48

Table 45: Boron-BINOL mediated aza Diels-Alder reaction using an assortment of achiral additives.

We also employed simple aliphatic alcohols with isopropanol resulting in an enantiomeric excess of 50% ee, clearly showing that a wide range of structurally diverse alcohols had a positive effect on the enantioselectivity ofthese type of room temperature aza Diels-Alder reactions. *N*-methylimidazole, which gave improved levels of stereocontrol when employed with Kobayashi's zirconium-BINOL system, gave no increase in enantioselectivity.[54] The hindered base diisopropylethylamine and dimethylsulfide were also used as additives with no improvement in enantioselectivity, indicating that these additives act as simple spectators in these aza Diels-Alder reactions. The last two additives used were dimethylsulfoxide, which gave a small increase to 38% ee and triethylphosphine oxide which surprisingly resulted in a 48% ee that is 15% greater than with standard conditions, which represented the only additive which gave similar levels of enhancements to alcohol additives.

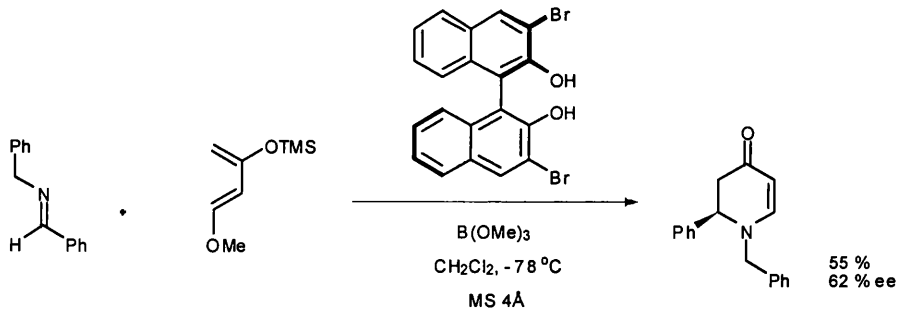
3.4 Modified BINOL ligands and the Aza Diels-Alder reaction

The enantiopurity that had been achieved for the asymmetric aza Diels-Alder reaction at – 78 °C appeared to have reached the maximum value possible when the parent BINOL-boron catalytic system was employed. At low temperature it had been shown that the achiral background reaction catalysed by $B(OMe)_3$ was not an issue so our aim of increasing the enantiomeric excess to >80% ee appeared impossible without fundamental changes to the chiral ligand. Therefore, it was decided that the next logical course of action was to modify the structure of the chiral BINOL ligand itself.

Yudin and colleagues have recently written an excellent review describing the use of modified BINOL ligands in asymmetric catalysis where they elucidate various synthetic routes to prepare different types of BINOL ligands and their success in asymmetric reactions.[124] Furthermore, several commercially available BINOL ligands are now available in enantiopure form, and as a consequence we first screened a selected number of these readily available ligands.

3.4.1 Commercially available BINOL-type ligands

The first modified ligand we investigated was (*R*)-3,3'-Br_2-BINOL, which is commercially available, although rather expensive at £620/g! The standard procedure was carried out at – 78 °C to prepare a BINOL-boron complex from 3,3'-Br_2-BINOL, which catalysed the aza Diels-Alder reaction to afford the desired pyridone in 62% ee and in 55% yield at - 78 °C (Scheme 111).



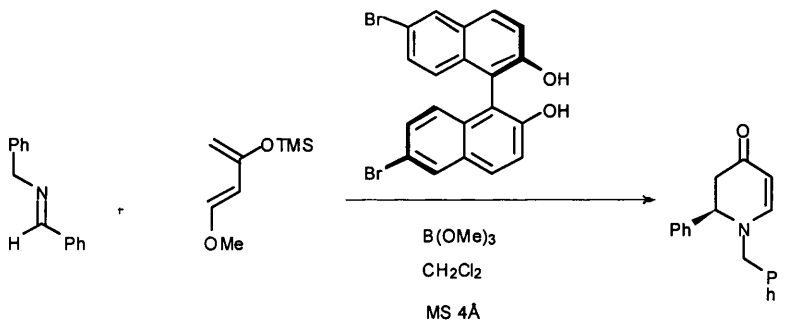
Scheme 111: Aza Diels-Alder reaction using a (*R*)-3,3'-Br_2-BINOL-boron complex.

This reaction at -78 °C using 3,3'-Br_2-BINOL-boron complex clearly resulted in a lower level of asymmetric induction of 62% ee, when compared to the 74% ee achieved using standard unsubstituted BINOL. The reaction was repeated at room temperature and gave an ee of 37%, which was a marginal improvement over the 33% ee achieved with BINOL. We also carried out a five hour slow addition reaction using 3,3'-Br_2-BINOL, which surprisingly gave a much lower ee of just 28%. This was unexpected, since it had been found that the use of BINOL as a ligand in the corresponding inverse addition reaction had resulted in a significant increase in enantiomeric excess had increased considerably (Table 46).

BINOL Ligand	*Method*	*Temperature, °C*	*Yield, %*	*ee, %*
3,3'-Br_2-BINOL	Standard	22	60	37
3,3'-Br_2-BINOL	Standard	- 78	55	62
3,3'-Br_2-BINOL	Inverse	22	25	28

Table 46: Aza Diels-Alder reaction using (*R*)-3,3'-Br_2-BINOL-boron complex.

The next ligand we employed was the (*R*)-6,6'-Br_2-BINOL ligand, which was commercially available and had been successfully used before in the Kobayashi laboratory for asymmetric aza Diels-Alder and Mannich reactions (Scheme 112).[54,55]



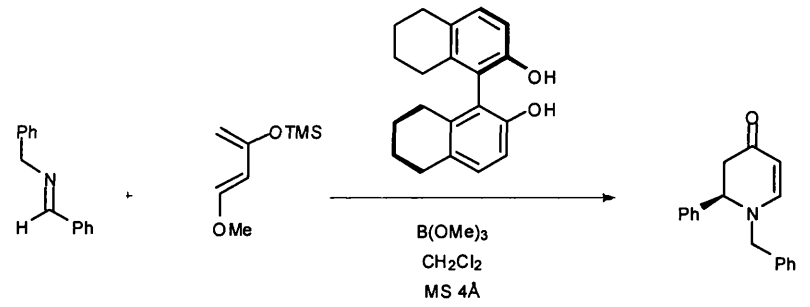
Scheme 112: Aza Diels-Alder reaction mediated by (*R*)-6,6'-Br_2-BINOL-boron complex.

The yields obtained in these reactions when 6,6'-Br_2-BINOL ligand was employed showed no increase when compared to the 3,3'-Br_2-BINOL-boron complex with the reaction at -78°C affording a 60% ee. The reaction at room temperature gave dihydropyridone in only 23% ee, whilst the slow 5 hour inverse addition methodology failed to afford any product at all (Table 47).

BINOL Ligand	*Method*	*Temperature, °C*	*Yield, %*	*ee, %*
6,6'-Br_2-BINOL	Standard	22	57	23
6,6'-Br_2-BINOL	Standard	-78	56	60
6,6'-Br_2-BINOL	Inverse	22	Failed	Failed

Table 47: Aza Diels-Alder reaction mediated by (*R*)-6,6'-Br_2-BINOL-boron complex.

The final commercially available ligand we used in our BINOL-boron mediated aza Diels-Alder reaction was a partially hydrogenated ligand known as H_8-BINOL, which had been used successfully by Renaud and co-workers in conventional Diels-Alder reactions.[125]



Scheme 113: Asymmetric aza Diels-Alder reaction mediated by (*R*)-H_8-BINOL-boron complex.

The first reaction was carried out using two equivalents of (*R*)-H_8-BINOL with one equivalent of trimethyl borate at room temperature to mediate the aza Diels-Alder reaction, which gave racemic pyridone (Scheme 113). It was speculated that perhaps the H_8-BINOL ligand was not coordinating to form a chiral boron complex leaving just trimethyl borate to catalyse the reaction, hence affording a racemic product. This theory was substantiated by carrying out the reaction at -78 °C, which resulted in no product being formed whatsoever, which is indicative of trimethyl borate failing to act as a Lewis Acid at this temperature (Table 48). We then modified the reaction so that one equivalent of (*R*)-H_8-BINOL was used as an additive in the presence of one equivalent of (*R*)-BINOL and one equivalent of trimethyl borate, in an inverse reaction at room temperature which gave dihydropyridone in only 34% ee.

BINOL Ligand	*Additive*	*Method*	*Temperature, °C*	*Yield, %*	*ee, %*
H_8-BINOL	None	Standard	22	11	RAC
H_8-BINOL	None	Standard	-78	Failed	Failed
H_8-BINOL	(*R*)-BINOL	Inverse	22	50	34

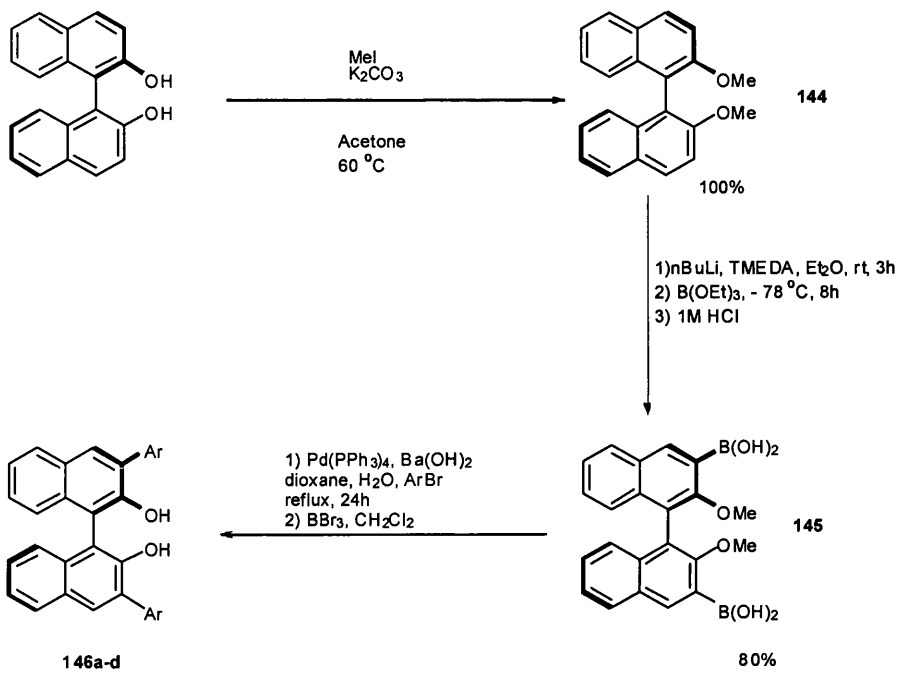
Table 48: Aza Diels-Alder reactions using (*R*)-H_8-BINOL and trimethyl borate.

Clearly, the use of these commercially available modified BINOL's as ligands for formation of chiral boron-BINOL complexes had resulted in a decrease in enantiomeric excess when compared to the use of BINOL alone. Consequently, it was decided to prepare a series of buttressed BINOL ligands containing aryl substituents at their 3 and 3' positions, in the hope that they might afford better stereocontrol.

3.4.2 Synthesised BINOL ligands

Given that the commercially available BINOL type ligands screened had not resulted in any advantage over the standard BINOL ligand it was decided to prepare a series of buttressed BINOL type ligands. Methodology developed by Jørgensen *et al*, was therefore used to synthesise a range of 3,3' aryl disubstituted BINOL's to examine their effects on the enantioselectivity and yield of the aza Diels-Alder reaction.[126]

The first step carried out was to protect the hydroxyl functionalities of BINOL by refluxing BINOL with MeI and K_2CO_3 overnight, which afforded the methylated BINOL **144** in quantitative yield. Treatment of methylated BINOL **144** with BuLi/TMEDA resulted in bis-*ortho* lithiation, followed by quenching with triethylborate to afford the desired bis-boronic acid BINOL **145** in 80% yield. Boronic acid **145** was then treated with $Pd(PPh_3)_4$, $Ba(OH)_2$ and a range of aromatic halides in refluxing dioxane/water to afford 3,3'-disubstituted BINOL's, which were subsequently demethylated via treatment with BBr_3 to yield the desired BINOL ligands **146a – 146d** (Scheme 114).



Scheme 114: Synthesis of 3,3'-disubstituted BINOL's.

The table below shows the results obtained from the Suzuki coupling reaction of a series of four aryl bromide coupling partners (Table 49), which gave moderate yields, whilst the cross coupling of 2-hydroxy bromobenzene failed to proceed.

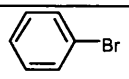
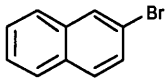
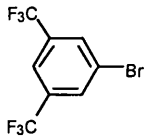
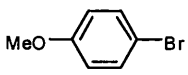
ArBr	*Product*	*Yield, %*
	**146a**	68
	**146b**	65
	**146c**	60
	**146d**	45

Table 49: Results for the Suzuki cross-coupling reactions.

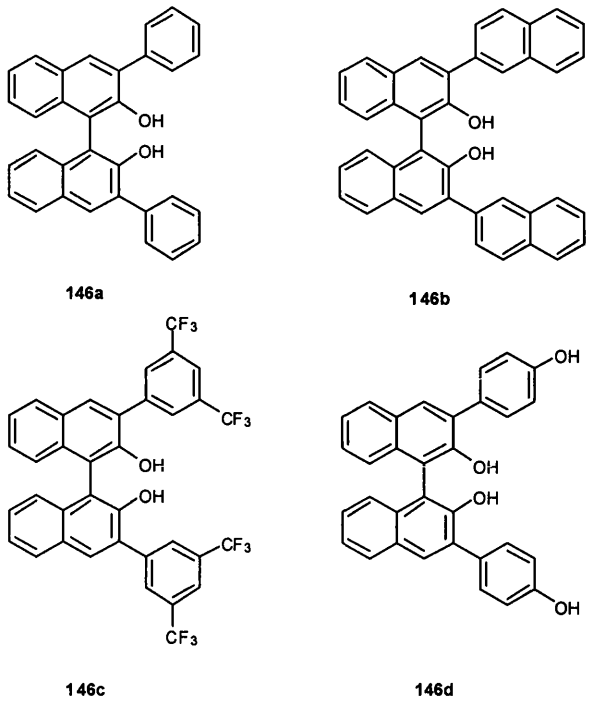
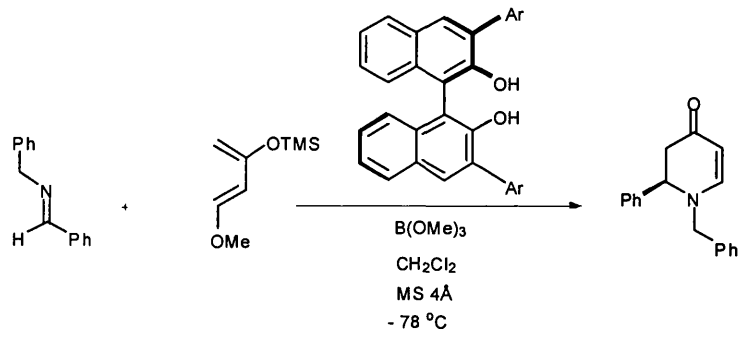


Figure 40: Range of ligands synthesised for the boron-BINOL aza Diels-Alder reaction.

This series of 3,3'-disubstituted ligands were then screened in the boron-BINOL mediated aza Diels-Alder reaction carried out at – 78 °C (Scheme 115).



Scheme 115: Dihydropyridone formation using modified BINOL-type ligand.

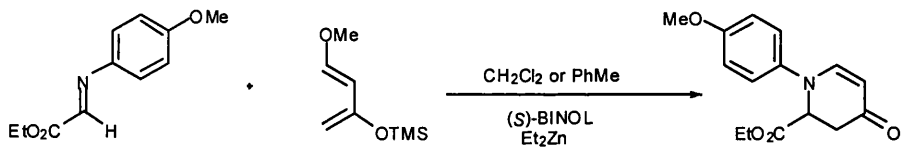
Ligand	*Yield, %*	*ee, %*
146a	45	10
146b	Failed	Failed
146c	70	18
146d	90	18

Table 50: Aza Diels-Alder reaction using modified BINOL ligands.

The table shows how the use of the aryl ligand **146a** resulted in a reduced yield and a much reduced 10% ee for pyridone formation indicating that the extra steric bulk at the 3 and 3' positions was clearly detrimental to this catalytic system. The bis 3,3'-naphthyl-BINOL ligand **146b** resulted in no pyridone formation, whilst the ligand **146c** which contained electron withdrawing trifluoromethyl groups within the 3,3'-aromatic fragments also resulted in a substantially reduced ee of 18%. The final ligand employed **146d** interestingly gave the greatest yield of dihydropyridone achieved by us for this aza Diels-Alder reaction with a yield of 90%, however the enantioselectivity of 18% ee was prohibitively low.

3.5 Effect of solvent on the boron-BINOL mediated aza Diels-Alder reaction

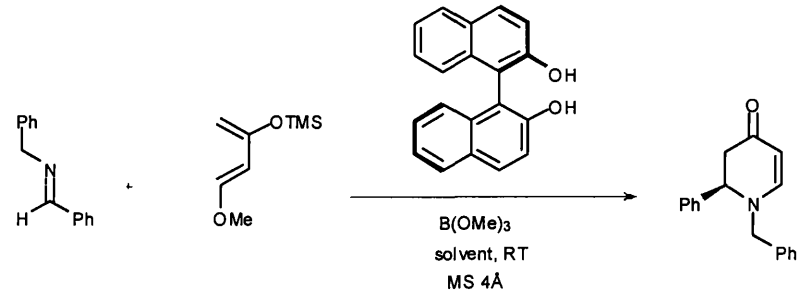
The aza Diels-Alder reaction under investigation had always been performed in dichloromethane or occasionally in chloroform. In a recent paper published by Whiting *et al.* they described a related aza Diels-Alder reaction which was initially carried out in dichloromethane, however they found that higher levels of enantioselectivity were obtained when the solvent was changed to the less polar toluene resulting in an increase to 84% ee at room temperature.[63] In their case, the reaction took much longer than in dichloromethane and interestingly higher enantioselectivity occurred at room temperature rather than at - 78 °C (Scheme 116).



Scheme 116: Aza Diels-Alder reaction using BINOL-zinc complex in various solvents.

3.5.1 Aza Diels-Alder reaction in toluene

The first reaction that was carried out was the usual aza Diels-Alder reaction of Danishefsky's diene with benzylidenebenzylamine with the standard BINOL-boron complex made from mixing (*R*)-BINOL with trimethyl borate in a 2:1 ratio. This time however the reaction was carried out in dry toluene at room temperature (Scheme 117).



Scheme 117: Boron-BINOL mediated aza Diels-Alder reaction carried out in different solvents.

This reaction formed the desired pyridone in a slightly lower than typical 52% yield, however the enantiomeric excess was significantly better than when the same reaction was carried out in methylene chloride, up from 33% to 45% ee. The same reaction was then repeated at -78 °C to examine the effect on enantioselectivity and once again we achieved a slight increase from 74% to 77% when carried out in toluene.

In light of these improved results we attempted a 5 h slow inverse addition, where trimethyl borate was added over a 5h period using a syringe pump at room temperature. This reaction only gave 35% ee in toluene, somewhat lower than when compared to the same reaction in methylene chloride, where a 62% ee is obtained.

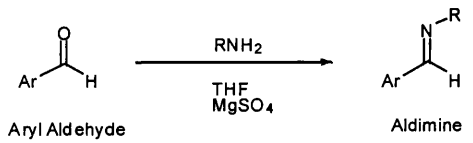
Solvent	*Temperature, °C*	*ee, %*
CH_2Cl_2	22	33
PhMe	22	**45**
CH_2Cl_2	- 78	74
PhMe	- 78	**77**
THF	- 78	22
Et_2O	22	33

Table 51: Comparison of the enantioselectivities obtained using different solvents for the aza Diels-Alder reaction.

The fact that the use of toluene instead of methylene chloride gave an increase in enantiomeric excess at room temperature, is probably due to the achiral background reaction being slower and less effective in less polar solvents like toluene. We also carried out this aza Diels-Alder reaction in tetrahydrofuran at -78 °C, resulting in a poor 22% ee, whilst diethyl ether at room temperature gave a 33% ee which was comparable with the use of dichloromethane (Table 51).

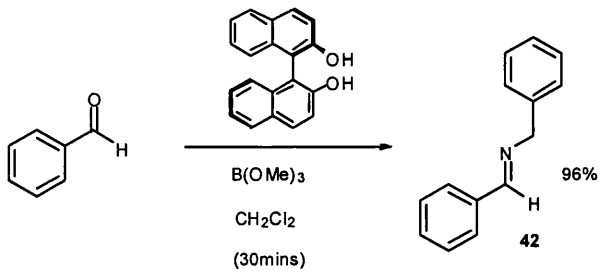
3.6 Three component methodology for the aza Diels-Alder reaction

The standard aza Diels-Alder reaction normally used to synthesise chiral pyridones involves reaction of a preformed aldimine with Danishefsky's diene mediated by a boron-BINOL Lewis acid complex. These aldimines are readily prepared by reacting a primary amine with an aryl aldehyde in THF over magnesium sulphate (Scheme 118).



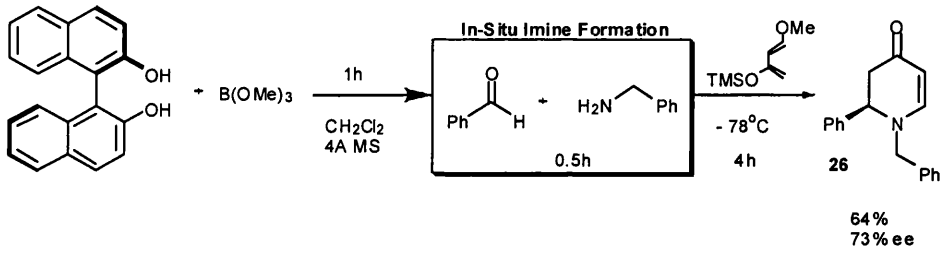
Scheme 118: Simple condensation reaction between aldehyde and amine to form aldimine product.

It was decided that it would be very convenient if a protocol could be devised whereby imine formation would occur *in situ* in the same reaction vessel as the aza Diels-Alder reaction was occurring, thus effectively removing one step from the synthesis. It was shown that whilst aldimine formation occurs fairly rapidly in THF, that the corresponding uncatalysed reaction in methylene chloride or toluene was very slow (2 days). Imine condensations are known to work well in the presence of a Lewis acid however, so we tested the condensation of benzaldehyde and benzylamine, in the presence of the boron-BINOL complex (2eq. BINOL: 1eq. $B(OMe)_3$) in dichloromethane to form benzylidenebenzylamine **42** (Scheme 119).



Scheme 119: BINOL-boron Lewis acid catalysed imine formation.

This imine condensation reaction occured almost quantitatively over a short period of time of >1h. So the next step was to carry out the boron-BINOL catalysed aza Diels-Alder reaction using benzylamine and benzaldehyde as substrates to form the desired pyridone **26** (Scheme 120).

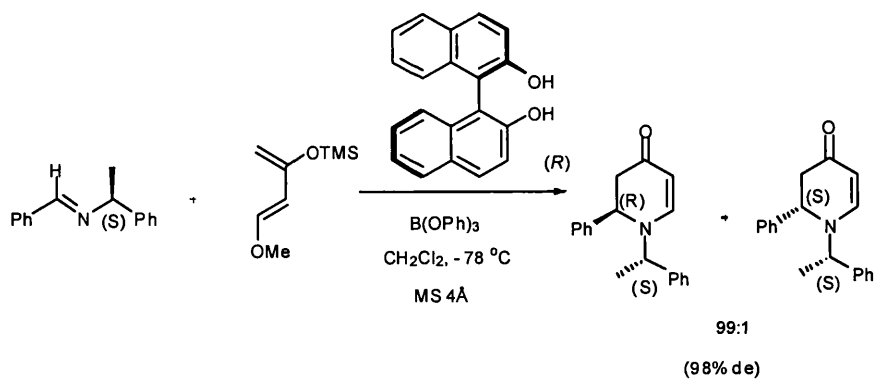


Scheme 120: One pot three component boron-BINOL mediated aza Diels-Alder reaction.

The 'one-pot' three component reaction gave the desired pyridone in 64% yield and 73% ee, which was comparable to the standard two component reaction using preformed imine. It is proposed that the water evolved in the imine condensation is rapidly absorbed by the 4Å molecular sieves and hence does not effect the outcome of the aza Diels-Alder reaction. This methodology would therefore allow for further substrate screening without the need to synthesise the desired imine substrate separately.

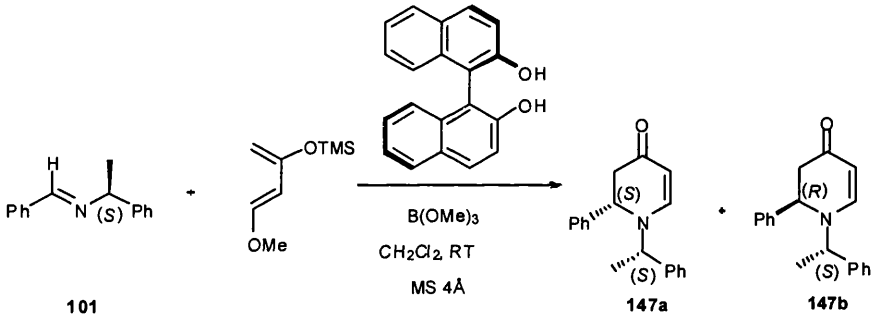
3.7 Synthesis of pyridones derived from chiral imines

As a natural extension into the investigation of the boron-BINOL mediated aza Diels-Alder reactions it was decided to examine the effect of using enantiomerically pure imines. Yamamoto had previously shown that when (*S*)-benzylidene-α-methybenzylamine was reacted with Danishefsky's diene at – 78 °C then a high diastereomeric excess could be achieved (Scheme 121).[24]



Scheme 121: The aza Diels-Alder reaction using a chiral imine.

We carried out a series of three aza Diels-Alder reactions using a boron-BINOL reagent generated from two equivalents of BINOL and one equivalent of trimethyl borate, using the (*S*) enantiomer of benzylidene-α-methylbenzylamine at room temperature using both enantiomers of BINOL, as well as with trimethyl borate as the Lewis acid catalyst in a similar manner to Yamamoto (Scheme 122).



Scheme 122: Room temperature aza Diels-Alder reaction using chiraly pure imine.

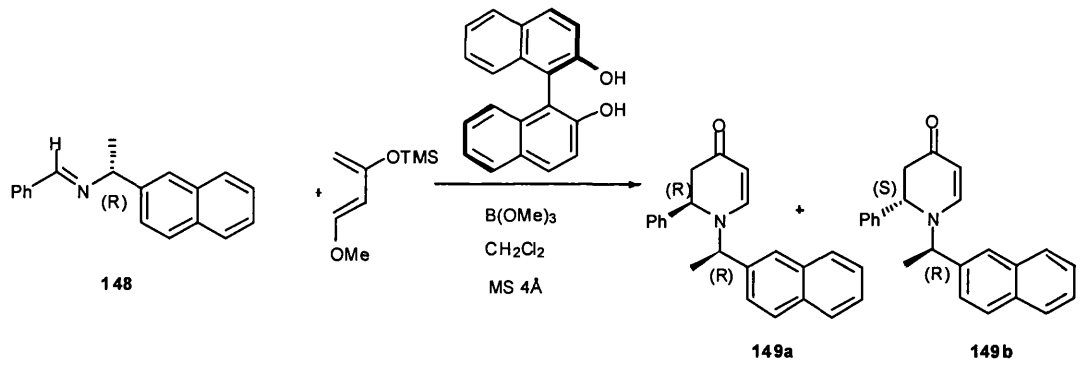
Yamamoto had shown that the use of (*S*)-imine and the (*R*)-BINOL-boron complex gave the highest level of stereocontrol at – 78 °C affording the (2*R*,*S*) diastereomer in 98% de. It was decided to carry out the same procedure at room temperature to investigate whether the optimisation studies described earlier could be of benefit to this type of diastereoselective reaction. The aza Diels-Alder reaction with Danishefsky's diene was carried out using (*S*)-**101** employing both enantiomers of BINOL, racemic BINOL as ligands of the boron catalyst. It was found that the diastereoselectivity of the (2*S*,*R*) diastereomer formed was enhanced when using (*R*)-BINOL at room temperature

affording the dihydropyridone in 52% de. This was expected as Yamamoto had previously shown that the combination of (*R*)-BINOL with (*S*)-**101** represented the matched pair coupling. This was confirmed by carrying out the aza Diels-Alder reaction at room temperature, using (*S*)-BINOL and (*S*)-imine which gave the (2*R*,*S*)-diastereoisomer in 32% de.

boron-BINOL reagent	*Imine stereochemistry (128)*	*de, % (129a)*
R	*S*	52
S	*S*	32
RAC	*S*	36

Table 52: Room temperature aza Diels-Alder reaction using (*R*)-benzylidene-α-methybenzylamine.

Finally we studied the aza Diels-Alder reaction using a 2-naphthyl derived imine **148** and Danishefsky's diene mediated by the BINOL-boron reagent to examine whether a naphthyl fragment of the auxiliary would give a greater level of diastereoselectivity (Scheme 123).



Scheme 123: Aza Diels-Alder reaction between chiral imine and Danishefsky's diene.

This time the reaction was carried out at both room temperature and -78 °C using both enantiomers of BINOL using the (*R*)-enantiomer of the 2-naphthyl derived imine **148** (Table 53).

Boron-BINOL Reagent	*Imine stereochemistry*	*Temperature, °C*	*de, % (131b)*
R	*R*	22	34
S	*R*	22	60
RAC	*R*	22	45
R	*R*	- 78	37
S	*R*	-78	74

Table 53: Results from the aza Diels-Alder reaction using (*R*)-2-naphthyl derived chiral imine.

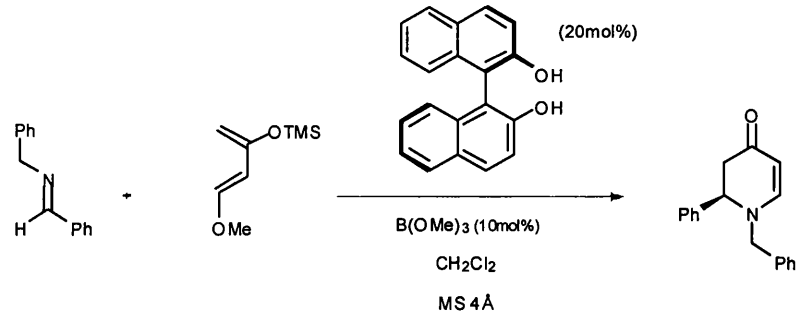
The table shows that with this reaction the expected (*S,R*)-diastereomer **149b** is afforded in excess when compared to the diastereomer **149a**. When the reaction is carried out at -78 °C a moderate 74% de is achieved when using the (*S*)-BINOL-boron reagent. Employing the (*R*)-BINOL-boron reagent gave a poor 34% de as expected, whilst the racemic form gave 45% de, showing the effect relayed from the chiral centre in place on the imine fragment. The naphthyl based auxiliary showed a slightly higher level of diastereoselectivity when compared to the phenyl based auxiliary at room temperature, however at – 78 °C the diastereoselectivity was significantly lower. Once again the diastereomers formed were confirmed by ^{1}H NMR.

3.8 The catalytic boron-BINOL mediated aza Diels-Alder reaction

All of the boron-BINOL mediated aza Diels-Alder reactions of aldimines with Danishefsky's diene carried out to date had employed the BINOL-boron Lewis acid as a stoichiometric reagent. One of the major goals of this project was to develop a boron-BINOL catalysed aza Diels-Alder reaction that employed lower catalyst loadings. To date there are few examples of catalytic aza Diels-Alder reactions with the exception of Kobayashi *et al.* who successfully used a BINOL-zirconium chiral Lewis acid catalyst for both aza and carbonyl Diels-Alder reaction with only catalytic loading.[54] Therefore, investigations were carried out to determine whether the catalyst loading of the boron-BINOL Lewis acid could be reduced to sub-stoichiometric levels,

3.8.1 Reactions using 10 mol% of a boron-BINOL complex

The first reaction investigated was the use of 10 mol% of boron-BINOL complex in the aza Diels-Alder reaction between Danishefsky's Diene and benzylidenebenzylamine at room temperature and – 78 °C (Scheme 124).



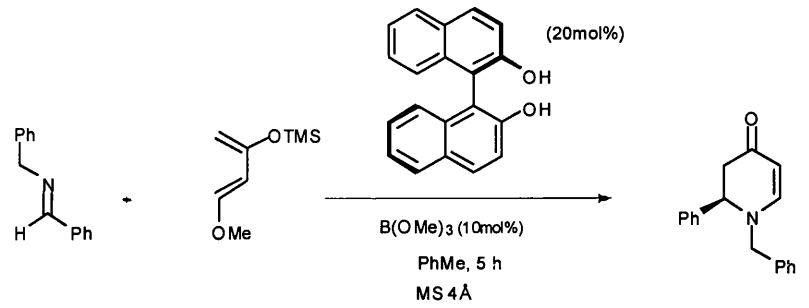
Scheme 124: Catalytic aza Diels-Alder reaction using 10mol% BINOL-boron Lewis acid.

The procedure for these reactions involved the use of 0.1 eq of trimethyl borate and 0.2 eq. (*R*)-BINOL for catalyst formation. The results of the 10 mol% catalyst reaction at room temperature showed a slightly improved enantioselectivity of 39% ee when compared to the use of a stoichiometric amount of catalyst (33% ee). The yield of dihydropyridone was reduced to 44% however, but this value was clearly much greater than the 10 mol% of catalyst employed in the reaction indicating true catalytic turnover had occurred (Table 54).

Loading, mol %	*Temperature, °C*	*Yield, %*	*ee, %*
100	22	62	33
10	22	44	39
100	0	63	47
10	0	42	44
100	- 78	70	74
10	- 78	37	47

Table 54: Comparison between 10mol% and stoichiometric loading at various temperatures.

At – 78 °C the enantioselectivity of 47% found when 10 mol% boron-BINOL catalysts was much lower than the 74% ee obtained when stoichiometric amounts of catalyst were employed, although the 37% yield of dihydropyridone produced demonstrated that catalytic turnover had occurred.



Scheme 125: Catalytic aza Diels-Alder reaction carried out in toluene.

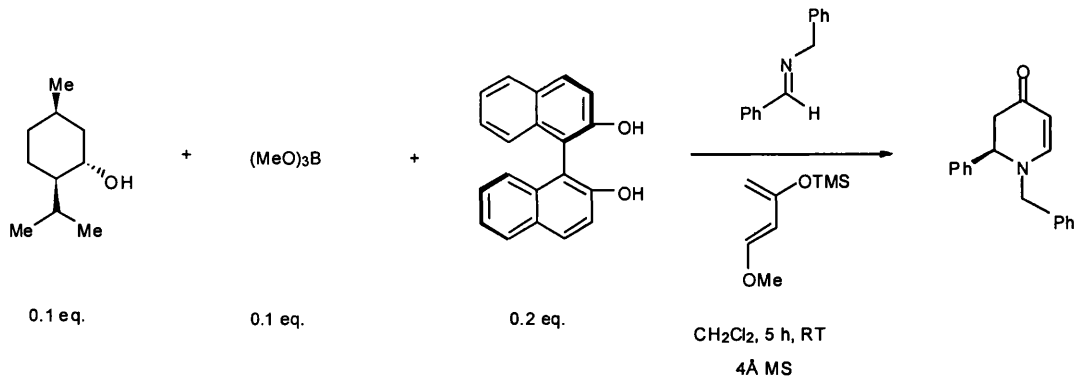
Two aza Diels-Alder reactions were then carried out using toluene as a solvent at - 78 °C and room temperature however, in both cases the enantioselectivities were much lower when 10mol% BINOL-boron complex was used than when compared to using stoichiometric amount of catalyst (Table 55). The enantioselectivities obtained were also lower than the values obtained for these reactions in methylene chloride, whilst the yield of the pyridone remained <40%.

Loading, mol%	*Temperature, °C*	*Yield, %*	*ee, %*
100	22	52	45
10	22	35	32
100	- 78	77	40
10	- 78	30	25

Table 55: Aza Diels-Alder reaction in toluene at various temperatures and at – 78 °C.

3.8.2 Catalytic reactions with *iso*-menthol

The next attempt to devise a truly catalytic asymmetric aza Diels-Alder reaction was to carry out the reaction in the presence of the chiral additive *iso*-menthol. In previous experiments, the use of stoichiometric amounts of BINOL-boron Lewis acid and *iso*-menthol had afforded higher enantioselectivities at room temperature. It was proposed that the use of catalytic quantities of *iso*-menthol might also lead to higher levels of enantioselectivity when 10 mol% of boron-BINOL complex was employed (Scheme 126).



Scheme 126: Catalytic aza Diels-Alder reaction using *iso*-menthol additive.

We therefore carried out this asymmetric aza Diels-Alder reaction using 10 mol% boron-BINOL complex in the presence of either 0.1 eq. or 1 eq. of *iso*-menthol at room temperature. Examination of the results from Table 56 reveal that the addition of *iso*-menthol had little effect on either the yield or enantioselectivity of the 10 mol% catalyst reaction.

Boron-BINOL Complex	*Iso-Menthol Additive, mol%*	*Temperature, °C*	*Yield, %*	*ee, %*
100	100	22	61	52
10	10	22	45	40
10	100	22	48	36
10	0	22	44	39

Table 56: Catalytic aza Diels-Alder reaction using the chiral additive *iso*-menthol.

To summarise, it is clear that asymmetric aza Diels-Alder reactions can be carried out at room temperature and at – 78 °C using 10 mol% of boron-BINOL catalyst however in both cases the yield and ee of dihydropyridone product are inferior to those obtained when stoichiometric amounts of catalyst are employed. However, the 30 to 50% yield of dihydropyridone product obtained clearly indicate that significant turnover of the 10 mol% catalyst is occurring in these reactions, thus offering the opportunity to develop catalytic aza Diels-Alder reactions in the future.

3.9 Summary of new approaches to the boron-BINOL mediated aza Diels-Alder reaction

In this chapter we have explored several modifications to the standard boron-BINOL mediated aza Diels-Alder reaction between Danishefsky's diene and benzylidenebenzylamine. When the reaction is carried out at - 78 °C we have managed to increase the yield of the pyridone from a lowly 41% yield to a healthy 75% when two equivalents of Danishefsky's diene are used for reaction. Slight increases in enantiomeric excess of dihydropyridone produced from 74% to 77% have been achieved at -78 °C using toluene as a solvent instead of methylene chloride.

Our biggest gains have been achieved carrying out the aza Diels-Alder reaction at room temperature. Initial experiments involving the use of stoichiometric amounts of chiral catalyst in CH_2Cl_2 afforded dihydropyridone in 33% ee, however the use of alcohol additives such as *iso*-menthol resulted in an increase to 52% ee. It was then demonstrated that the competitive achiral background catalysed by $B(OMe)_3$ could be suppressed by using a slow inverse addition technique that resulted in an enantiomeric excess for dihydropyridone formation of 62% ee.

We have also shown that the boron-BINOL catalyst could be used catalytically, however the level of asymmetric induction were inferior to the yields and ee obtained when stoichiometric quantities of catalyst are employed. In the next chapter my investigations into the use of Kauffman's C_3-symmetric boronate species as a catalyst for the asymmetric aza Diels-Alder reaction will be described.

4 Results and Discussion 3: A C_3-Symmetric Catalyst for the Asymmetric aza Diels-Alder Reaction

4.1 Introduction

In the previous two chapters the investigations into optimising the preparation of the boron-BINOL chiral catalyst and it use for the asymmetric aza Diels-Alder reaction of imines have been described. Whilst carrying out these studies it was noted that mixing BINOL and trimethyl borate for extended periods of time resulted in the formation of a small amount of a new species that was identified as a C_3-symmetric boron-BINOL complex that was first reported by Kaufmann *et al.*[127] In this chapter we describe our investigations into the use of this C_3-symmetric boron-BINOL complex as a catalyst for the asymmetric aza Diels-Alder reaction of imines with Danishefsky's diene.

4.2 Initial ^{1}H NMR investigations

In chapter two it was described how the various substrates present in the boron-BINOL mediated aza Diels-Alder reaction were subjected to a range of ^{1}H NMR experiments. Specifically it was shown that when two equivalents of BINOL were mixed with one equivalent of trimethyl borate over short periods of time that no new species was observed. This was surprising as it was expected that a dimeric or possibly a monomeric boron-BINOL complex would have been formed under these conditions and it was concluded that a boron-BINOL complex formed only in the presence of imine. However, it was found that when a solution of BINOL and trimethyl borate were left to stand overnight in dichloromethane in the presence of 4Å MS that a new boron-BINOL species was formed in around 10% yield (Appendix 1.4). Examination of the ^{1}H NMR spectra of this new complex, which displayed diagnostic resonances at δ6.64, enabled it to be identified as the C_3-symmetric propeller boronate **117** first identified by Kaufmann *et al.* (Figure 41).[100,127]

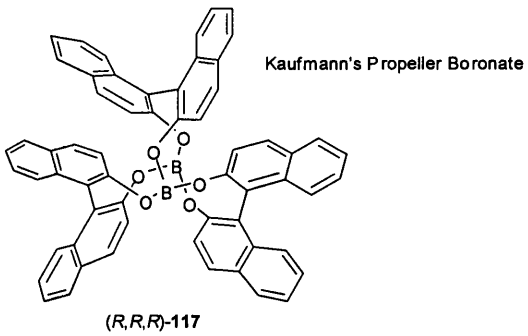
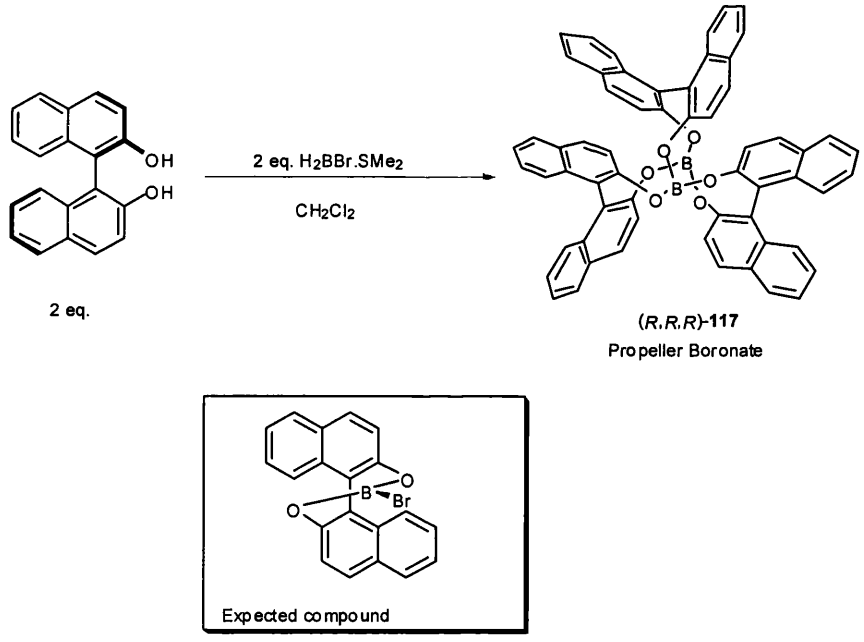


Figure 41: Kauffman's propeller boronate catalyst.

4.3 Studies within the Kauffmann laboratory

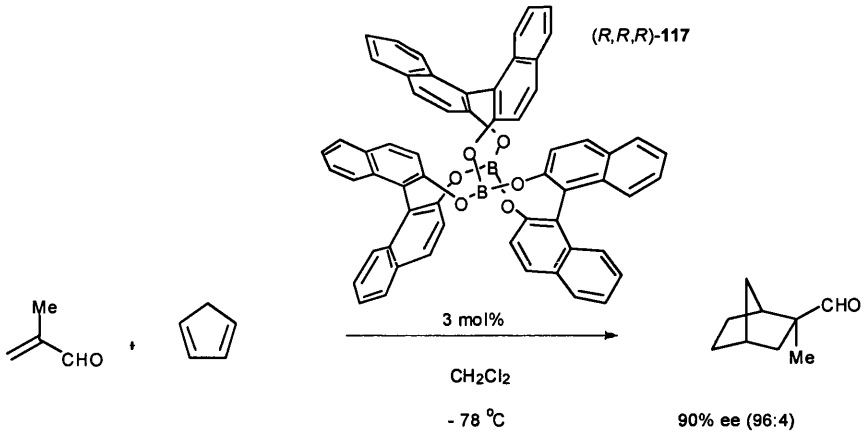
In 1990 Dieter Kaufmann and Roland Boese accidentally synthesised the C_3-symmetric tetradecacyclic diboronate **117** by combining two equivalents of BINOL and monobromoborane dimethylsulfide.[127] The propeller structure of the boronate complex was identified by X-ray crystallography, and was shown to be comprised of two boron atoms and three equivalents of BINOL (Scheme 127).



Scheme 127: Kauffman's first synthesis of propeller boronate **117**.

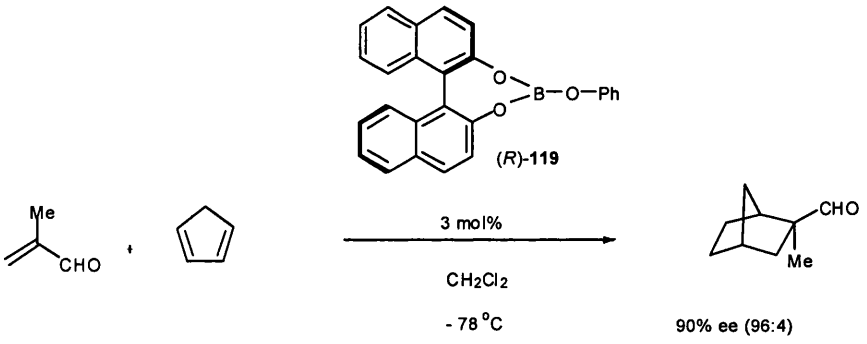
Kaufmann had previously developed halo-organoborane catalysts and applied them successfully in asymmetrically induced Diels-Alder reactions. Therefore, he screened the propeller boronate **117** as a catalyst in the Diels-Alder reaction of methacrolein and

cyclopentadiene at – 78 °C, which resulted in the formation of the cycloadduct in 85% yield with 97% *exo* selectivity and an enantioselectivity of 90% ee (Scheme 128).



Scheme 128: Diels-Alder reaction catalysed by propeller boronate **117**.

Kaufmann also reported that the Diels-Alder reaction of methacrolein and cyclopentadiene using a monomeric BINOL borate **119**, prepared in a similar manner to Yamamoto, proceeded with identical levels of enantioselectivity and yield as when using the propeller boronate **117** (Scheme 129). This was particularly interesting given that Yamamoto had originally proposed that this monomeric boronate **119** was the active catalyst in the boron-BINOL catalysed asymmetric aza Diels-Alder reaction of benzylidenebenzylamine and Danishefsky's diene.[24] Monomeric boronate **119** was not isolated by either Yamamoto or Kaufmann, and consequently structure of this 1:1 complex has not been proven to our satisfaction.

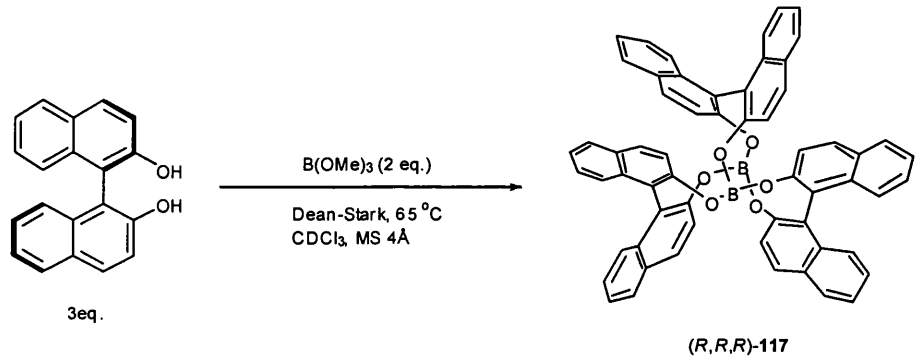


Scheme 129: Diels-Alder reaction catalysed by monomeric boron-BINOL species **119**.

4.4 Synthesis of the C_3-symmetric propeller boronate

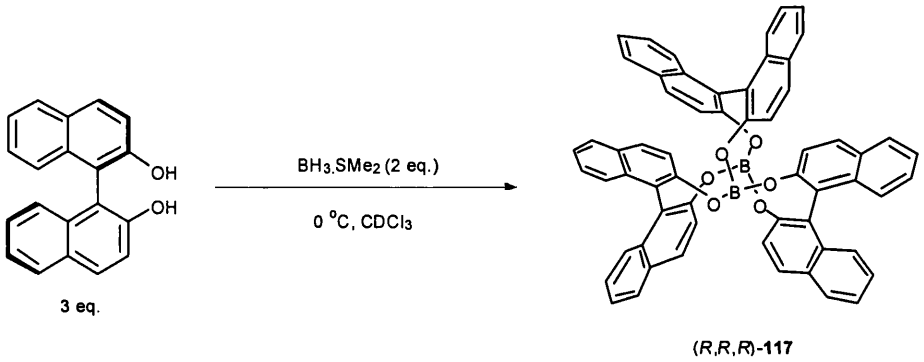
Since Kaufmann had shown that the propeller boronate species was a suitable catalyst for standard Diels-Alder reactions, and we had found evidence for its formation in our

aza Diels-Alder reaction, it was proposed that this species should be prepared and screened as a potential catalyst for the aza Diels-Alder reaction. The first approach for its synthesis involved refluxing two equivalent of trimethyl borate with three equivalents of BINOL using a Dean-Stark apparatus whose side arm contained 4Å molecular sieves to remove methanol produced in the complexation reaction. The reaction was carried out using $CDCl_3$ as a solvent to allow easy monitoring by ^1H NMR spectroscopic analysis, and required two days to proceed to completion, with the molecular sieves being replaced after 24 hours. ^1H and ^{13}C NMR spectroscopic analysis showed the successful formation of the propeller boronate species in quantitative yield (Scheme 130). This complex proved to be extremely moisture sensitive, rapidly decomposing on standing in air and as a consequence it was stored and used as a solution in $CDCl_3$.



Scheme 130: Formation of propeller boronate **117** using the Dean-Stark method.

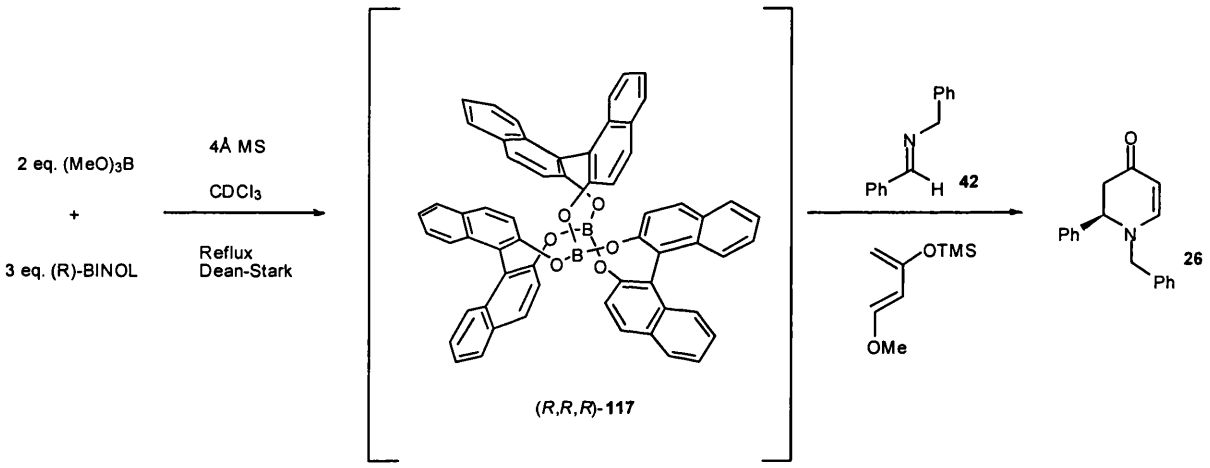
The synthesis of C_3-symmetric complex **117** was also carried out using the method described by Kaufmann, which involved mixing three equivalents of BINOL with two equivalents of borane dimethylsulfide complex in either chloroform or dichloromethane at 0 °C. Once again the propeller boronate could be obtained in excellent yield as a solution in dichloromethane or chloroform due to the stability of the species, however in this case dimethylsulfide remained present as an additive in these solutions (Scheme 131).



Scheme 131: Formation of propeller boronate from BINOL and borane dimethylsulfide.

4.5 Aza Diels-Alder reaction and the propeller boronate

This propeller boronate complex was then screened as a catalyst for the asymmetric aza Diels-Alder reaction. First we tested the propeller boronate **117** synthesised from refluxing BINOL and trimethyl borate in $CDCl_3$. Imine **42** was added to a solution of C_3-propeller boronate in $CDCl_3$ in the presence of 4Å molecular sieves followed by addition of Danishefsky's diene at room temperature (Scheme 132).

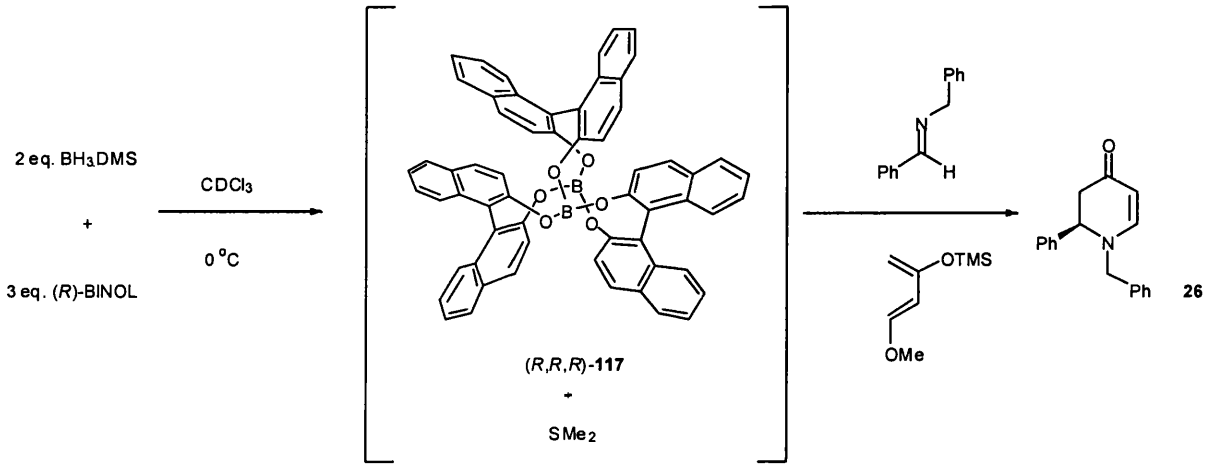


Scheme 132: Synthesis of pyridone using propeller boronate catalyst.

Borate	*Temperature, °C*	*Yield, %*	*ee, %*
Standard	22	62	33
Propeller	22	69	48
Standard	- 78	70	74
Propeller	- 78	72	74

Table 57: Preparation of pyridone **26** using BINOL propeller borate and Yamamoto's boron-BINOL Lewis acid.

The propeller boronate catalyst clearly showed an improvement at room temperature affording dihydropyridone **26** in 48% ee which represents a 15% increase in ee at room temperature when compared to the standard boron-BINOL type catalyst used previously, with a slight increase in yield to 69%. These results were equally encouraging at – 78 °C as we observed an identical 74% ee for the dihydropyridone formation. We next examined this aza Diels-Alder reaction using the propeller boronate prepared using borane dimethylsulfide, which had the potential to afford different results due to the presence of residual dimethylsulfide as a potential additive (Scheme 133).



Scheme 133: Propeller species catalysed the aza Diels-Alder reaction.

Borate	*Temperature, °C*	*Yield, %*	*ee, %*
Standard	22	62	33
Propeller + SMe_2	**22**	**67**	**63**
Standard	- 78	70	74
Propeller + SMe_2	- 78	70	71

Table 58: Preparation of pyridone **26** using propeller boronate synthesised from borane and the standard boron-BINOL system.

Table 58 shows that a solution of the propeller boronate solution prepared by Kaufmann's method, which contained dimethylsulfide, afforded dihydropyridone **26** in 63% ee at room temperature in an improved 67% yield. This clearly provides a synthetic advantage in this asymmetric reaction, since the desired dihydropyridone could now be obtained in >60% ee at room temperature. It is important to note that a

standard boron-BINOL mediated aza Diels-Alder reaction carried out in the presence of 1 equivalent of dimethylsulfide afforded dihydropyridone **26** in only 42% ee. Unfortunately, when the aza Diels-Alder reaction was carried out using this DMS-propeller boronate solution at – 78 °C we observed no increase in enantioselectivity when compared to the standard boron-BINOL reaction conditions.

Given that both the propeller boronate catalyst and the original boron-BINOL catalyst mediated aza Diels-Alder reaction affording the desired dihydropyridone in similar yields it was proposed that the same active species might have been formed in both reactions. Indeed, the enantioselectivity of both catalyst preparations for aza Diels-Alder reactions at – 78 °C is essentially identical, as observed previously by Kaufmann for convential Diels-Alder reactions!

4.6 Kaufmann's propeller boronate and imine NMR investigations.

Since Kaufmann's propeller boronate catalyst had been shown to mediate the aza Diels-Alder reaction of Danishefsky's diene and various imines, it was decided to investigate the course of this reaction by NMR spectroscopy. Therefore, the ^{1}H NMR spectra of the propeller boronate complexed to imine **42** was acquired which revealed a mixture of imine **42**, propeller boronate and a new species displaying a AB quartet at δ_H 4.19 ppm after 10 minutes.

After one day of complexation this new species referred to as species **A** was clearly evident showing a diagnostic AB quartet centred at δ 4.15 ppm, which was diagnostic of the diastereotopic *N*-benzyl protons of the imine complexed to a chiral boron-BINOL species (Figure 42).

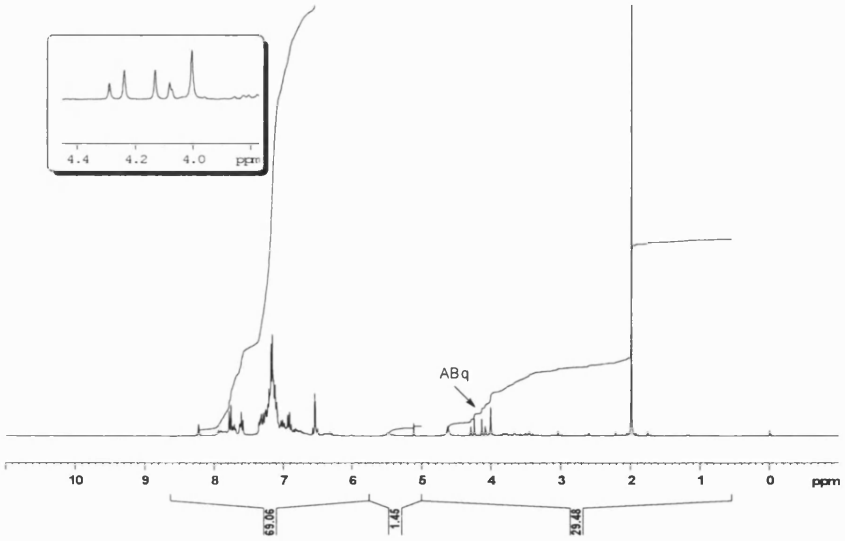


Figure 42: ^{1}H NMR spectrum showing the formation of species **A**.

When this mixture was left for five days all of the original propeller boronate complex was consumed and a series of new species were formed with a white solid precipitating from solution. This white solid was filtered off and a ^{1}H NMR spectra obtained in deuterated acetonitrile, which revealed a new boron-BINOL based complex which we refer to as species **B**. An AB quartet centred δ3.5 ppm could be observed in its NMR spectrum which was once again clearly indicative of diastereotopic protons of imine benzylic protons in a chiral environment (Figure 43).

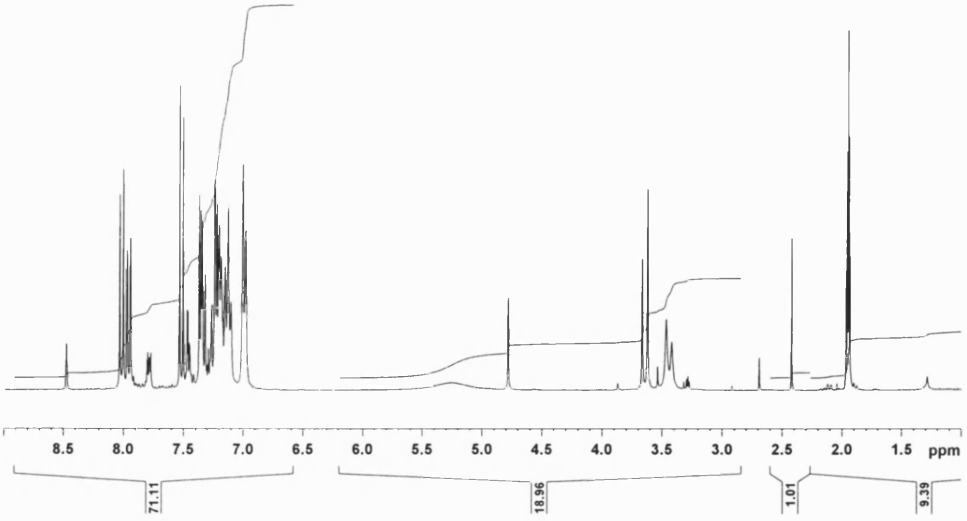


Figure 43: ^{1}H NMR showing the solid formed (**B**) after 5days.

The most interesting species formed arose from mixing stoichiometric quantities of the propeller boronate complex **117** with imine **46** in CH_2Cl_2 containing a small amount of hexane. After the solution was left overnight, a white solid precipitated out (reffered to as species **C**) whose ^1H NMR spectrum was acquired which also showed an ABq centred at δ3.2 ppm. This species appeared to be similar to species **B** except the imine resonance could not be observed. Unlike species **B**, species **C** was soluble in $CHCl_3$ and therefore the spectra was acquired in $CDCl_3$ (Figure 44). The ^{11}B NMR spectra of this complex showed a resonance at δ 9.9ppm, indicating an sp^3 'ate' like boron species.

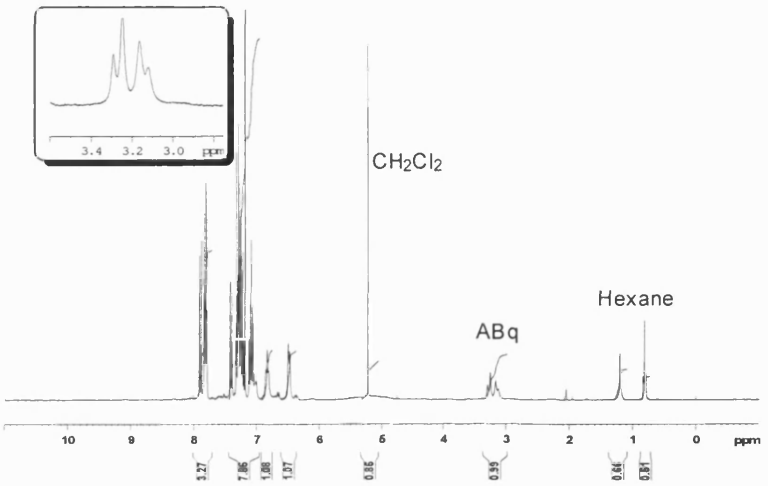


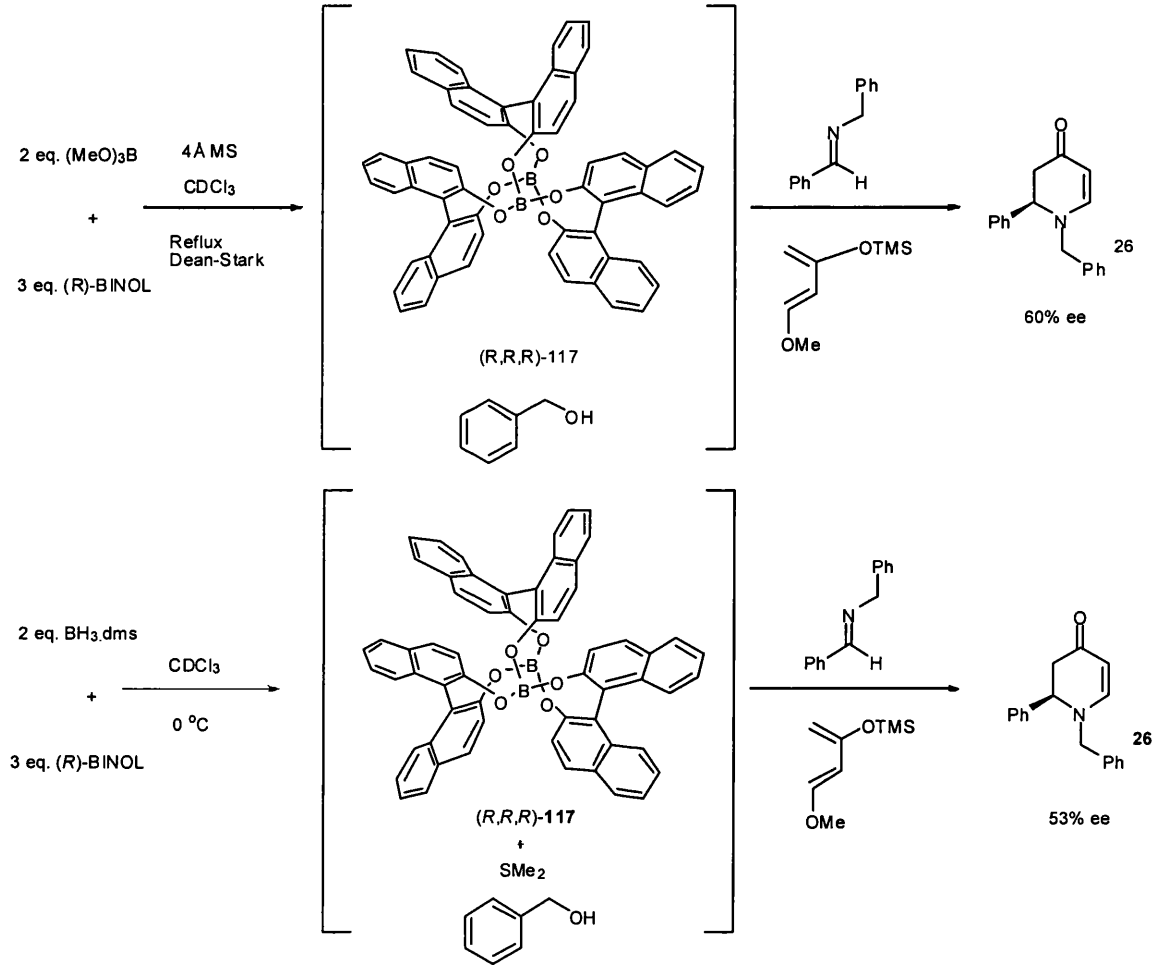
Figure 44: 1H NMR showing solid precipitated (**C**) when imine and propeller borate are mixed.

These NMR investigations show that mixing the propeller boronate with imine **42** results in a range of different species being formed over time. Species **A** is clearly active for the aza Diels-Alder reaction, since its use affords a stereoselective aza Diels-Alder reaction at room temperature. We also carried out the aza Diels-Alder reaction using propeller boronate-imine complex **B** which proceeded at room temperature in 65% yield and a slightly reduced 58% ee. The crystalline complex **C** also catalysed the aza Diels-Alder reaction however it only gave dihydropyridone in 20% yield and 17 % ee. Therefore, we can conclude from these NMR investigations that a number of active species are possible, that can interconvert via dynamic ligand exchange and conclude that the propeller boronate is simply acting as an efficient pre-catalyst reservoir for generating the active catalytic species.

4.7 Further modifications to the propeller boronate mediated aza Diels-Alder reaction

4.7.1 Benzyl alcohol Additive

In this chapter we have shown that the highest enantioselectivities achieved at room temperature involved using BINOL propeller boronate **117**, which were prepared by reacting BINOL with borane dimethylsulfide at 0°C. Having shown that benzyl alcohol is an effective additive for the aza Diels-Alder reaction, it was decided to carry out this reaction using both forms of propeller boronate in the presence of one equivalent of benzyl alcohol (Scheme 134).



Scheme 134: Propeller boronate used in conjunction with benzyl alcohol additive.

Interestingly the addition of one equivalent of benzyl alcohol to the propeller boronate made from trimethyl borate and BINOL, resulted in an increase in enantioselectivity up from 48% ee to 60% ee. When benzyl alcohol was added to the propeller boronate made from borane the enantioselectivity was reduced from 63% ee to 53% ee. Therefore, addition of benzyl alcohol to a propeller boronate prepared from $B(OMe)_3$ resulted in an increase in ee at room temperature similar to that observed previously in the Yamamoto procedure, adding further evidence for the intermediacy of a common catalytic intermediate in these reactions.

4.7.2 Propeller boronates of modified BINOL's

Following on from the modified BINOL ligand described in the previous chapter, we investigated the use of analogous propeller boronate precatalysts shown in Figure 45.

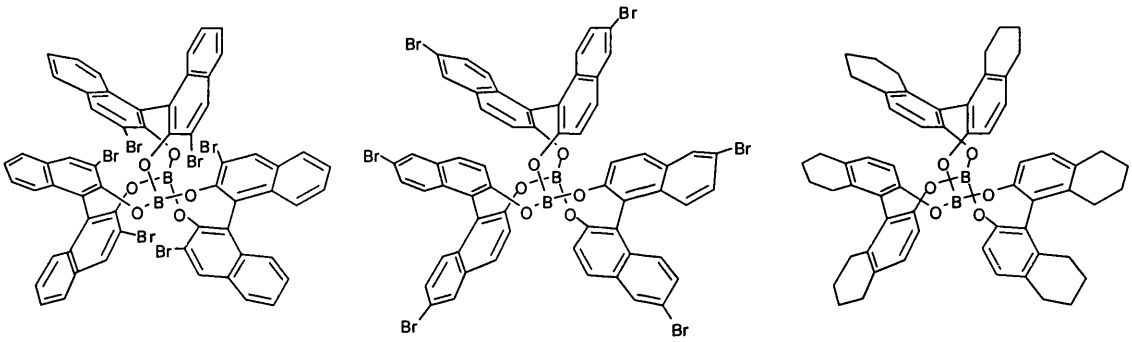


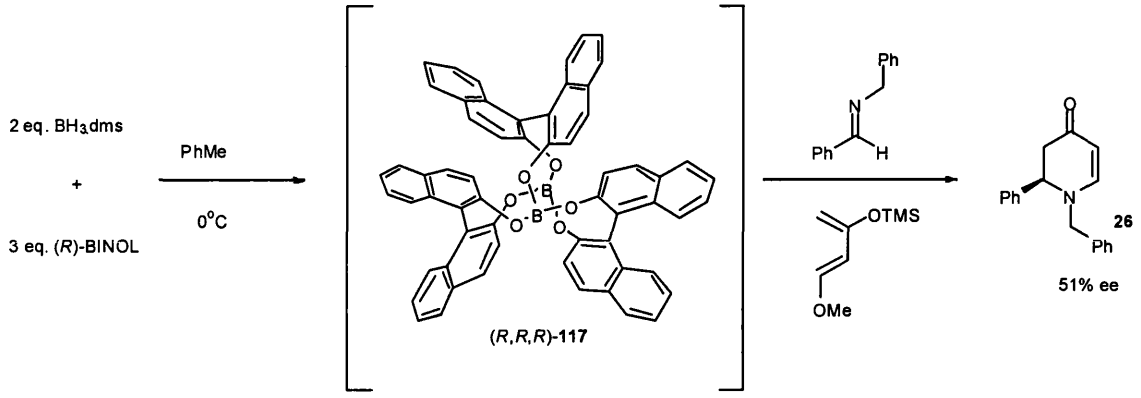
Figure 45: Potential new C_3-symmetric precatalysts for the asymmetric aza Diels-Alder reaction.

The attempted synthesis of all these complexes followed the same general procedure described above using 2 equivalents of borane and 3 equivalents of BINOL-type ligand. Unfortunately, none of these C_3-symmetric complexes could be formed, probably due to a combination of steric and electronic effects preventing efficient complexation in each case.

4.7.3 Propeller Boronate in Toluene

Given the increased enantioselectivity observed when toluene was used for the standard Yamamoto aza Diels-Alder reaction we attempted to synthesise the propeller boronate complex in dry toluene. Deuterated toluene was not used as a solvent because of cost considerations, however removal of an aliquot of the reaction mixture in toluene for ^1H NMR analysis revealed that the propeller boronate species could be synthesised in toluene. Danishefsky's diene was added to a solution of the propeller boronate and

benzylidenebenzylamine in toluene, which led to the desired pyridone product in 51% ee, at room temperature (Scheme 135). This ee was lower than the 63% ee obtained when chloroform was used as the solvent, however this value is still higher than when the standard Yamamoto boron-BINOL conditions were used.



Scheme 135: BINOL propeller boronate formed in toluene yields desired pyridone in 51% ee.

When the propeller boronate was used in toluene at – 78 °C the result was quite unexpected as the enantiomeric excess fell to only 39% ee in a poor yield 35 % (Table 59) which was lower than when compared with the same reaction carried out at room temperature. This result remains unexplained, but may be a consequence of low rates of ligand exchange in the non-polar solvents at boron at low temperatures. This would prevent formation of the reactive enantioselective complex, and thus explain the poor yield of reaction in non-polar solvent. It is possible that the presence of methanol in the Yamamoto procedure helps to catalyse the reactive complex at – 78 °C, thus explaining the difference in reactivity.

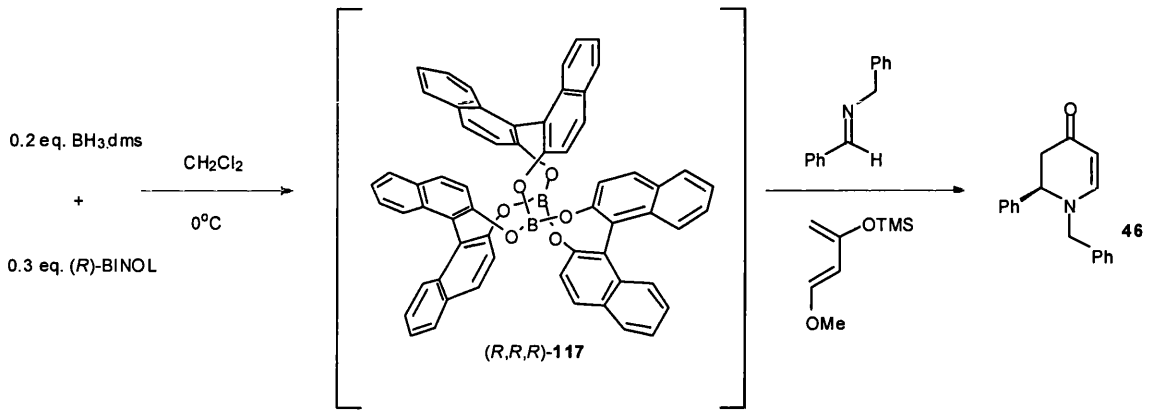
Solvent	*Method*[a]	*Temperature, °C*	*Yield, %*	*ee, %*
CH_2Cl_2	Standard	22	62	33
PhMe	**Standard**	**22**	**55**	**45**
CH_2Cl_2	Standard	- 78	70	74
PhMe	**Standard**	**- 78**	**49**	**77**
CH_2Cl_2	Kaufmann	22	67	63
PhMe	Kaufmann	22	39	51
CH_2Cl_2	Kaufmann	- 78	70	74
PhMe	Kaufmann	- 78	35	39

a) Standard method refers to Yamamoto's original condition applied at the described temperature. Kaufmann method refers to the use of BINOL propeller boronate synthesised from borane and BINOL for the aza Diels-Alder reaction.

Table 59: Comparison of dichloromethane with PhMe for the aza Diels-Alder reaction

4.7.4 Propeller boronate and the catalytic aza Diels-Alder reaction

It was decided to investigate whether the propeller boronate species could be used in sub-stoichiometric quantities as previously shown for the standard Yamamoto boron-BINOL catalyst (Scheme 136).



Scheme 136: Aza Diels-Alder reaction mediated by catalytic amounts of propeller boroate.

We carried out the aza Diels-Alder reaction using BINOL propeller boronate complex using dichloromethane as the solvent at room temperature and at – 78 °C (Table 60). In one case we used benzyl alcohol as an additive, given that we had previously shown that the use of stoichiometric amounts of propeller boronate and benzyl alcohol had given increased enantioselectivity when used together.

Propeller Boronate (mol%)	*Additive*	*Solvent*	*Temperature, °C*	*Yield, %*	*ee, %*
100	None	CH_2Cl_2	22	67	63
10	None	CH_2Cl_2	22	40	36
10	Benzylalcohol	CH_2Cl_2	22	31	30
100	None	CH_2Cl_2	- 78	70	74
10	None	CH_2Cl_2	- 78	39	50

Table 60: Aza Diels-Alder reaction using catalytic amounts of propeller boronate.

The table shows that using the propeller boronate catalyst to carry out the aza Diels-Alder reaction at room temperature in dichloromethane resulted in a significant drop in enantiomeric excess from 63% ee to 36% ee when 10 mol% of catalyst was used. The

addition of benzyl alcohol in this case had a detrimental effect on the reaction. Finally, when the reaction was performed in dichloromethane using 10 mol% of catalyst at - 78 °C we again found that the enantiomeric excess of 50% ee was significantly greater when stoichiometric amounts of propeller boronate were used (74% ee). However, the 30-50% yields of dihydropyridone produced in these reactions clearly reveal that catalytic turnover is occurring in these reactions.

4.8 Conclusions

In this chapter we have demonstrated how the use of C_3-symmetric propeller boronate species **117** offers an attractive route for the asymmetric synthesis of dihydropyridones via an aza Diels-Alder reaction. Most notably, our previous best enantioselectivities for this reaction have been further improved using this BINOL propeller boronate, which may act as an effective pre-catalyst, to generate the same stereoselective boron-BINOL catalyst previously generated using Yamamoto's original conditions. It is believed that this protocol generates a catalyst with no trimethyl borate present in the reaction, which results in an ee for standard dihydropyridone formation of 63% at room temperature. NMR spectroscopic studies substantiate the fact that an asymmetric complex containing two equivalents of BINOL is likely to be formed on reaction of the imine with the propeller boronate which then reacts with Danishefsky's diene to form the desired pyridone. The enantiomeric excesses obtained at – 78 °C appear to mirror the results of Yamamoto's original system at low temperature.

We have also shown that the propeller boronate system can be used catalytically in 10 mol%, however the level of asymmetric induction obtained are clearly inferior to those using stoichiometric quantities, as was found for the standard boron-BINOL system studied in the previous chapter. We have also experimented with other types of BINOL ligands, however these failed to form the desired C_3-symmetric propeller complexes. In the next chapter we investigate the versatility of this propeller boronate system by using it to catalyse the aza Diels-Alder reaction of a range of different substrates.

5 Results and Discussion 4: Substrate variation study

5.1 Aza Diels-Alder reactions of various imines

In the previous chapter it was successfully demonstrated how the boron-BINOL catalysts used for the aza Diels-Alder reaction of Danishefsky's diene and benzylidenebenzylamine could be optimised using a variety of techniques, and a new catalyst for this reaction was introduced in the form of the C_3-symmetric BINOL propeller boronate **117**.

It was therefore, important to investigate the scope and limitation of this methodology for a range of imine substrates, since it was possible that certain substrates might demonstrate higher levels of enantioselectivity in their aza Diels-Alder reactions. A screen of a wide range of substrates would also enable us to identify suitable natural product targets as candidates for this methodology which would then be synthesised to illustrate the potential of the boron-BINOL system.

Therefore, in this section I will describe how the asymmetric aza Diels-Alder reaction was applied to a range of different imines using boron-BINOL catalysts using a number of the optimisations strategies described in the previous chapters. This includes the use of Kaufmann's BINOL propeller borate[100] and the inverse slow addition method, both of which afforded marked improvements in enantioselectivity at room temperature. We will also demonstrate how a range of pyridones can be synthesised using the one pot three component reaction, foregoing the necessity for synthesising imine precursors. Finally the use of boron-BINOL catalysts to catalyse other reaction manifolds will be briefly described.

5.1.1 Substrate screening

A range of imines were chosen as substrates for the boron-BINOL mediated aza Diels-Alder reaction carried out at room temperature and – 78 °C. These imines were derived from a wide range of structural motifs, and were prepared from condensation of substituted benzaldehydes with aromatic or aliphatic amines. At this point in our investigation a number of natural product targets had been identified, hence some substrates were chosen specifically to generate suitable dihydropyridones for this purpose. Therefore, before carrying out aza Diels-Alder reactions the relevant imine

substrates had to be synthesised (Figures 46-48). This was achieved by mixing the corresponding aldehyde and amine in THF at room temperature, in the presence of magnesium sulfate as a dehydrating agent.

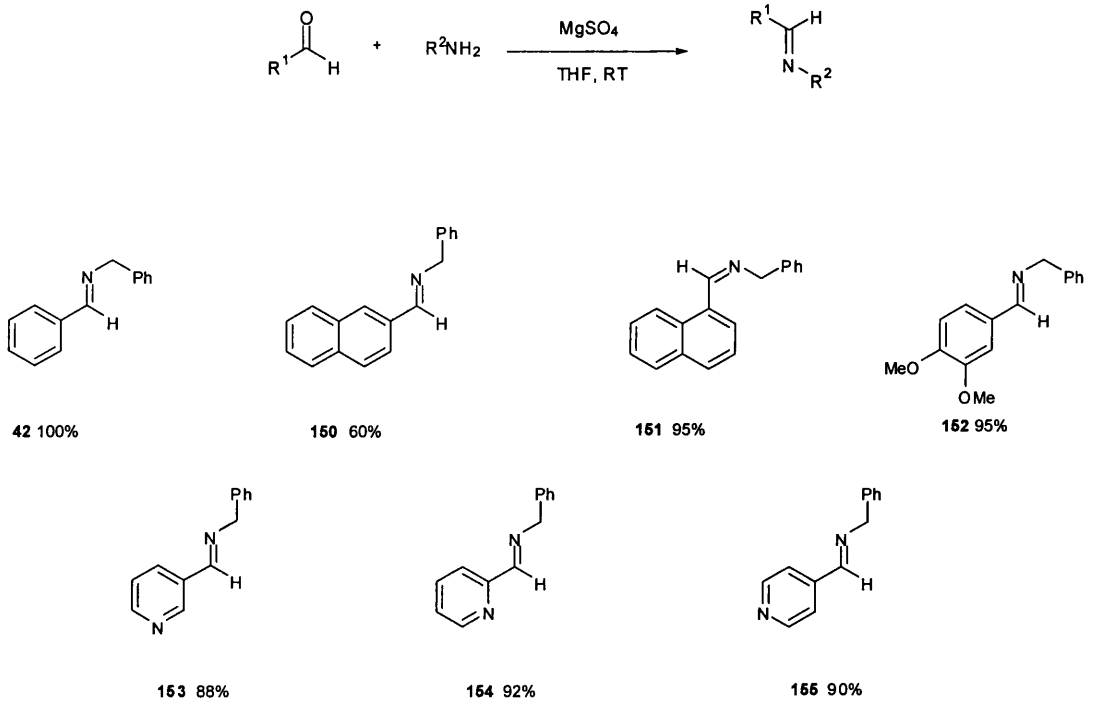


Figure 46: Imines derived from benzylamine and a range of aromatic aldehydes.

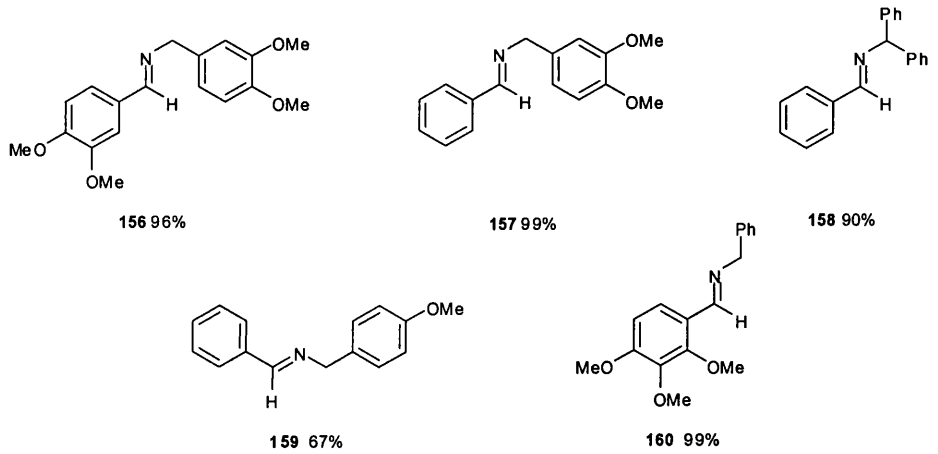


Figure 47: Imines derived from aromatic amines and aromatic aldehydes.

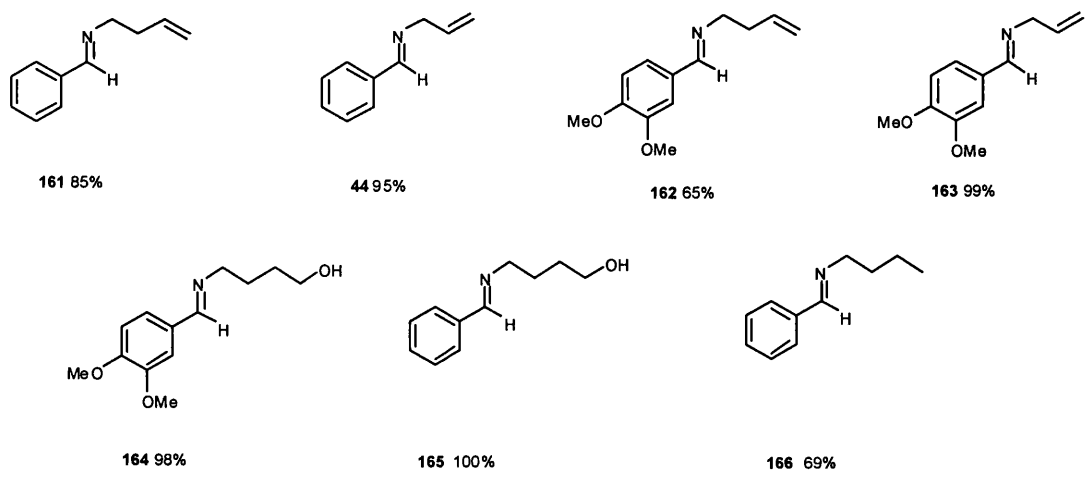
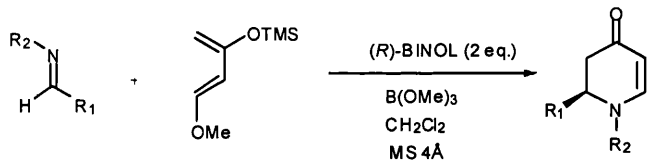
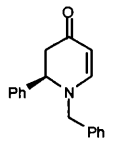
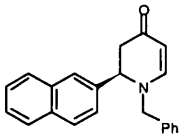
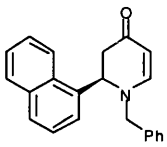
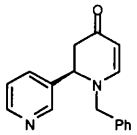
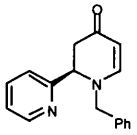
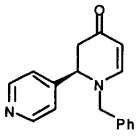
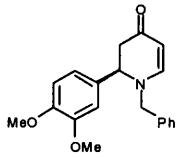


Figure 48: Imines derived from aliphatic amines.

These imines were then used in boron-BINOL catalysed aza Diels-Alder reactions under optimal conditions in which two equivalents of BINOL were premixed with one equivalent of trimethyl borate, in the presence of 4Å MS and the corresponding imine added followed by Danishefsky's diene. The results for a range of pyridones synthesised from the imines shown in Figure 46 are detailed below (Scheme 137, Table 61).



Scheme 137: Asymmetric aza Diels-Alder Synthesis of various pyridones from a range of imines and Danishefsky's diene.

Pyridone Product[a]	*Compound*	*Imine*	*Yield RT, %*	*ee*[b] *RT, %*	*Yield – 78 °C, %*	*ee – 78 °C, %*
	**26**	**42**	62	33	70	74
	**167**	**150**	50	42	65	82
	**168**	**151**	73	*rac*	85	*rac*
	**169**	**153**	52	58	60	83
	**170**	**154**	40	19	12	32
	**171**	**155**	36	*rac*	16	*rac*
	**172**	**152**	51	38	55	80

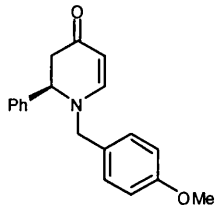
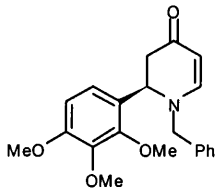
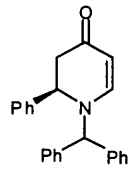
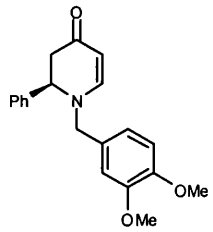
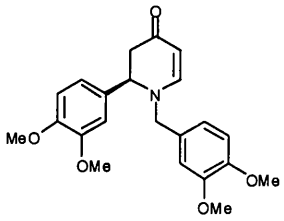
(a) Absolute configuration assigned by analogy with proven stereochemistry of known dihydropyridone ***26****, or via comparison with specific rotation with literature data.*

(b) Ee determined by chiral HPLC analysis and comparison with authentic racemic standards.

Table 61: Imine screen for the boron-BINOL catalysed aza Diels-Alder reaction.

The table shows that yields were generally higher when the reaction was carried out at - 78 °C when compared to room temperature, which we assume is due to the competing ability of BINOL to hydrolyse Danishefsky's diene at room temperature. The table shows that the enantioselectivity of the original aza Diels-Alder reaction to afford the parent dihydropyridone **26** ranks highly when compared to the other pyridones formed in this study. The pyridone that was formed with the greatest 82% ee at -78 °C was derived from an imine containing a 2-naphthyl substituent, however the imine derived

from the 1-naphthyl functionality remarkably exhibited no level of enantiocontrol. A similar situation occurred for pyridyl derived pyridones, whereby a high ee of 83% was obtained for 3-pyridyl-dihydropyridone **169**, with 2-pyridyl-dihydropyridone **170** showing only a 32% ee, whilst 4-pyridyl-dihydropyridone **171** was racemic. The pyridone containing the 3,4-dimethoxy substitution of **172** that was identified as a natural product synthon also showed a high level of enantioselectivity with an 80% ee achieved.

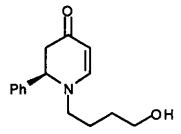
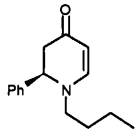
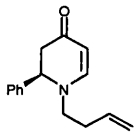
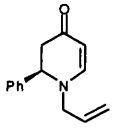
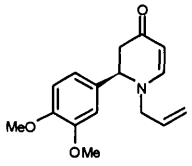
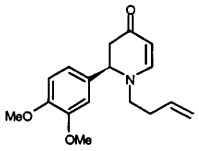
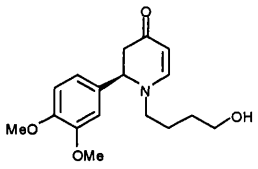
Pyridone Product[a]	*Compound*	*Imine*	*Yield RT, %*	*ee*[b] *RT, %*	*Yield – 78 °C, %*	*ee – 78 °C, %*
	**173**	**159**	34	ND	49	ND
	**174**	**160**	---	---	50	55
	**175**	**158**	11	ND	---	---
	**176**	**157**	25	ND	---	---
	**177**	**156**	65	55	73	81

(a) Absolute configuration assigned by analogy with proven stereochemistry of known dihydropyridone 26, or via comparison with specific rotation with literature data.

(b)Ee determined by chiral HPLC analysis and comparison with authentic racemic standards.

Table 62: Synthesis of pyridones from various imines using boron-BINOL catalyst.

Table 62 describes the yield and enantioselectivities achieved using imines derived from aromatic aldehydes and aromatic amines. Not all the above examples were carried out at both temperatures, however the generally observed trend that higher yields were achieved at lower temperatures was observed. In this case the dihydropyridone **177** showed the highest level of enantioselectivity, even obtaining 55% ee at room temperature.

Pyridone Product[a]	*Compound*	*Imine*	*Yield RT, %*	*ee*[b] *RT, %*	*Yield – 78 °C, %*	*ee*[b] *– 78 °C, %*
	**178**	**165**	65	*rac*	73	*rac*
	**179**	**166**	---	---	71	11
	**180**	**161**	---	---	17	55
	**181**[c]	**44**	60	27	65	77
	**182**	**163**	---	---	55	65
	**183**	**162**	5	13	10	*rac*
	**184**	**164**	52	*rac*	55	*rac*

*a) Absolute configuration assigned by anology with proven stereochemistry of known dihydropyridone **26**, or via comparison with specific rotation with literatuire data.*

b) Ee determined by chiral HPLC analysis and comparison with authentic racemic standards.

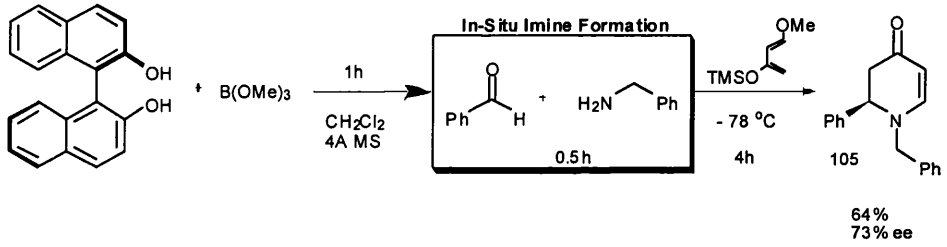
c) Carried out using triphenyl borate instead of the typical trimethyl borate.

Table 63: N-Alkyl-dihydropyridones derived from *N*-alkyl amines.

The aza Diels-Alder reactions to afford *N*-aliphatic pyridones generally exhibited lower ee's with the exception of dihydropyridones **181** and **182** which contain an *N*-allyl functionality (Table 63). The dihydropyridone **181** was afforded in 77% ee using triphenyl borate as a precursor, however *N*-butenyl variants generally gave much poorer ee's and yields, with *N*-aminobutanol variants affording racemic products, possibly due to competing coordination of the ω-OH group for boron preventing efficient catalyst formation.

5.1.2 The Three component methodology for the aza Diels-Alder reaction

In a previous chapter we investigated how the aza Diels-Alder reaction could be carried out in a 'one pot' three component fashion forgoing the need to synthesise the imine substrates in a separate step (Scheme 138).

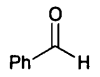
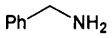
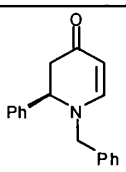
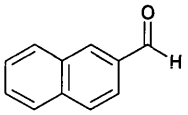
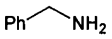
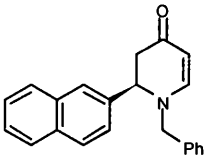
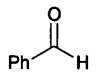
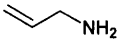
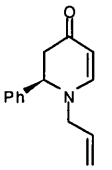
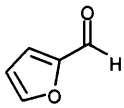
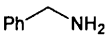
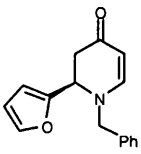
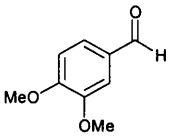
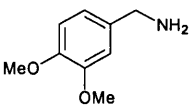
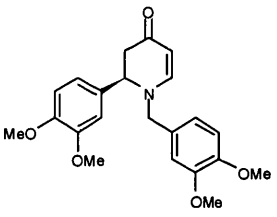
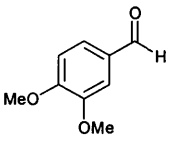
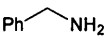
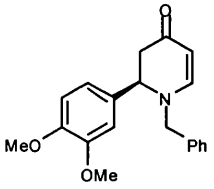
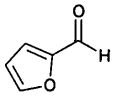
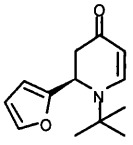
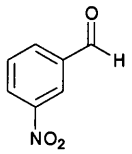
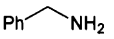
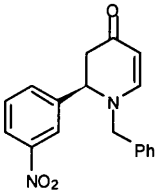


Scheme 138: One pot three component boron-BINOL mediated aza Diels-Alder reaction.

The potential of this methodology for synthesising a library of different pyridones, in a combinatorial manner at – 78 °C was therefore explored since this would represent a more efficient manner to prepare this class of heterocycle (*a) Absolute configuration assigned by anology with proven stereochemistry of known dihydropyridone **26**, or via comparison with specific rotation with literatuire data.*

b) Ee determined by chiral HPLC analysis and comparison with authentic racemic standards.

Table 64).

Aldehyde	*Amine*	*Dihydrpyridone*[a]	*Adduct*	*Yield, %*	*ee*[b]*, %*
			**26**	64	73
			**150**	64	82
			**181**	65	77
			**185**	30	UD
			**177**	55	81
			**172**	50	80
			**186**	Failed	---
			**187**	Failed	---

Reaction procedure as for scheme ***138*** *except* ***181*** *where* $B(OPh)_3$ *is used instead of* $B(OMe)_3$. *UD = undetermined.*

a) Absolute configuration assigned by anology with proven stereochemistry of known dihydropyridone **26**, *or via comparison with specific rotation with literatuire data.*

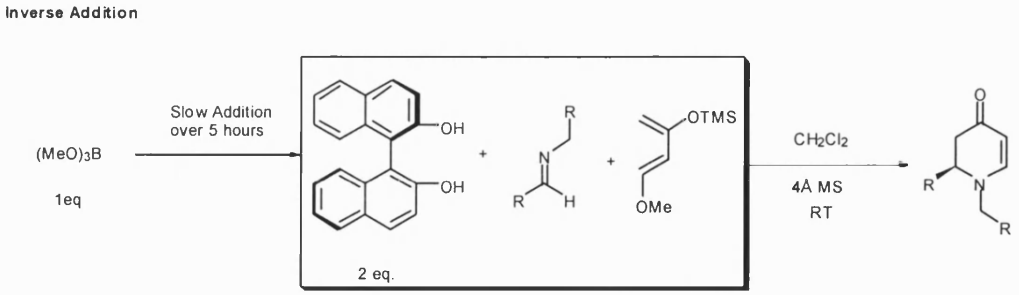
b) Ee determined by chiral HPLC analysis and comparison with authentic racemic standards.

Table 64: One pot three component variation on the boron-BINOL mediated aza Diels-Alder reaction.

The table above demonstrates how the three component variation of the aza Diels-Alder reaction could be employed to afford the same levels of enantiomeric excess as the stepwise protocol affording dihydropyridones in similar or slightly reduced yield. This modification certainly offers a quicker route for synthesising chiral dihydropyridones which would be a benefit when synthesising natural products containing a pyridone scaffold. Pyridones **186** and **187** were not formed under these conditions, showing that aryl imines containing electron withdrawing nitro groups, or sterically encumbered ^{t}butyl groups are not tolerated in this reaction.

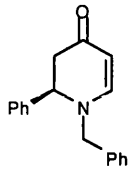
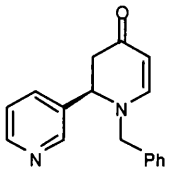
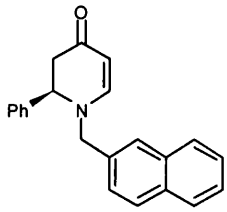
5.1.3 Inverse addition Methodology

In chapter three it was shown how an inverse addition protocol could be useful in affording higher levels of enantioselectivity when the boron-BINOL mediated aza Diels-Alder reaction was carried out at room temperature. We attributed this increased enantioselectivity to the effective suppression of the achiral background reaction mediated by free trimethyl borate. The procedure is practically simple and requires the addition of trimethyl borate to the other reaction components in a drop wise manner using a syringe pump set for a 5 h delivery time (Scheme 139).



Scheme 139: Diagrammatic representation of the inverse addition methodology.

To further test the inverse addition methodology we selected two further imine substrates for screening using this technique specifically **169** which had shown the highest levels of enantioselectivity of 83% ee at – 78 °C so far.

Dihydropyridone[a]	*Standard (RT) ee*[b]*, %*	*Standard (- 78 °C) ee*[b]*, %*	*Inverse (RT) ee*[b]*, %*
	33	74	62
	58	83	72
	42	82	40

*a) Absolute configuration assigned by anology with proven stereochemistry of known dihydropyridone **26**, or via comparison with specific rotation with literatuire data.*

b) Ee determined by chiral HPLC analysis and comparison with authentic racemic standards.

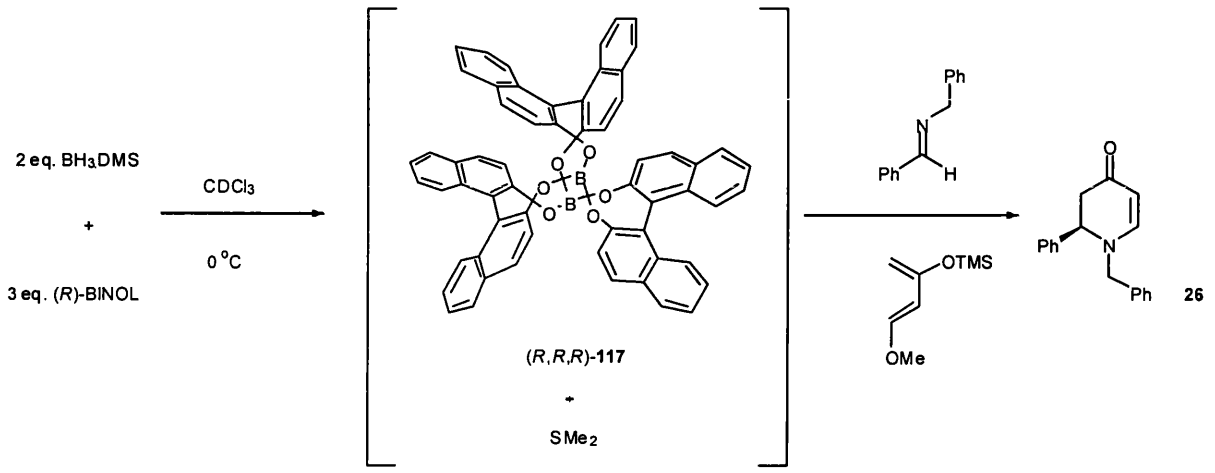
Table 65: Comparison of substrates for the inverse addition methodology.

Table 65 above shows how the inverse addition technique significantly increased the level of asymmetric induction of the room temperature reaction for the 3-pyridyl pyridone and the parent dihydropyridone, although these enantioselectivities are somewhat lower when compared to a standard reaction at – 78 °C. The 2-naphthyl derived pyridone unfortunately showed no increase in enantioselectivity when employing this methodology. The 3-pyridyl based dihydropyridone obtained in an ee of 72% represents the highest level of enantioselectivity so far achieved at room temperature.

5.1.4 Propeller boronate substrate investigation

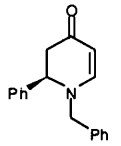
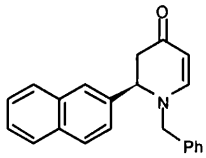
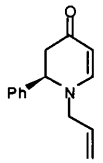
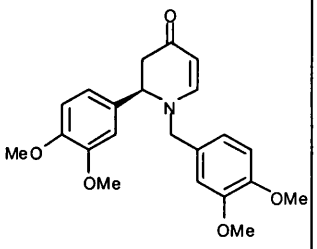
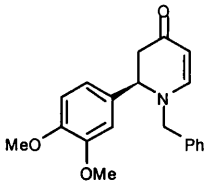
We have shown in the previous chapter that the C_3-symmetric propeller boronate is a novel catalyst that is useful for catalysing aza Diels-Alder reactions. It was

demonstrated how enantioselectivities for the aza Diels-Alder reaction of aldimines and Danishefsky's diene matched that of Yamamoto's protocol at – 78 °C and showed a significant enhancement in ee at room temperature (Scheme 140) with slightly higher yields of pyridone being attained.



Scheme 140: Propeller boronate as a catalyst for the aza Diels-Alder reaction.

In order to study the feasibility of the propeller boronate as a catalyst for the aza Diels-Alder reaction we investigated its use as a catalyst for the aza Diels-Alder reaction of a number of imines at room temperature as shown in Table 66 below.

Pyridone Product[a]	*Yield, % (RT) Standard Prep[b]*	*ee[c], % (RT) Standard Prep*	*Yield, % (RT) Propeller boronate*	*ee[c], % (RT) Propeller boronate*
	62	33	67	63
	50	42	55	43
	60	27	62	32
	65	55	70	62
	51	38	55	56

*a) Absolute configuration assigned by anology with proven stereochemistry of known dihydropyridone **26**, or via comparison with specific rotation with literatuire data.*

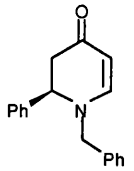
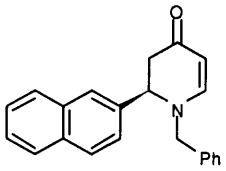
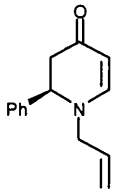
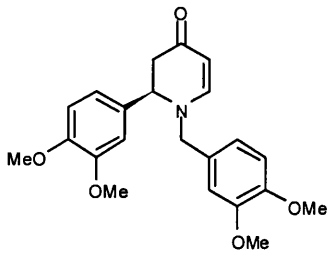
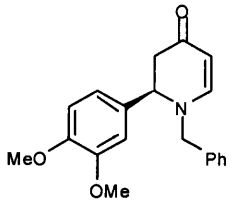
b) Standard prep refers to the original Yamamoto literature preparation using $B(OMe)_3$.[24]

c) Ee determined by chiral HPLC analysis and comparison with authentic racemic standards.

Table 66: Propeller boronate employed as a catalyst for the aza Diels-Alder reaction on a range of imine substrates at room temperature.

It is clear to see that the propeller boronate offered an increase in yield of dihydropyridone product across the board. Also, the enantioselectivities achieved were higher when compared to the standard reaction conditions for the boron-BINOL

catalysed aza Diels-Alder reaction. In some cases the increase was approaching 20 - 30% ee, which is highly significant. In other cases such as for the formation of the 2-naphthyl and *N*-allyl dihydropyridones we observed only a slight increase in enantioselectivity. In all cases though there was an increase. Given these results we also carried out the same comparison using an aza Diels-Alder reaction carried out at – 78 °C (Table 67).

Dihydropyridone[a] ***Product***	***Yield, % (- 78 °C)*** ***Standard Prep[b]***	***ee[c], % (- 78 °C)*** ***Standard Prep***	***Yield, % (- 78 °C)*** ***Propeller boronate***	***ee[c], % (- 78 °C)*** ***Propeller boronate***
	70	74	70	71
	65	82	83	88
	65	77	55	54
	73	81	75	77
	55	80	64	75

*a) Absolute configuration assigned by anology with proven stereochemistry of known dihydropyridone **26**, or via comparison with specific rotation with literatuire data.*

b) Standard prep refers to the original Yamamoto literature preparation using $B(OMe)_3$.[24]

c) Ee determined by chiral HPLC analysis and comparison with authentic racemic standards.

Table 67: Propeller boronate employed on a number of substrates at – 78 °C.

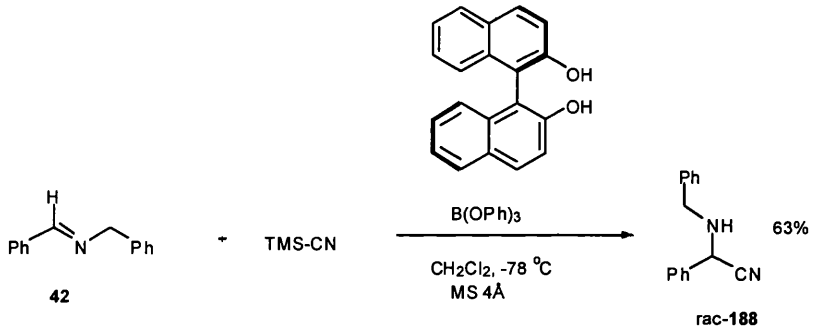
However, at – 78 °C, the results obtained were similar to those obtained employing the original Yamamoto conditions, although the 2-naphthyl pyridone afforded the highest enantioselectivity obtained of 88% ee.

5.2 Other reactions using the boron-BINOL reagent

The aza Diels-Alder reaction of activated dienes and imines described in this thesis is a synthetically useful carbon - carbon bond forming reaction, yielding key intermediates for a range of natural product syntheses.[128] There are however many more asymmetric carbon-carbon bond forming reactions that the boron-BINOL and propeller boronate catalysts could be screened against for stereoselectivity. These include an asymmetric Strecker reaction involving the addition of cyanide to an imine,[129] the reaction of silyl ketene acetals with imines in a Mannich fashion,[130] and the addition of silyl ketene acetals to enones.[131]

5.2.1 Strecker reactions mediated by a chiral boron-BINOL Lewis acid

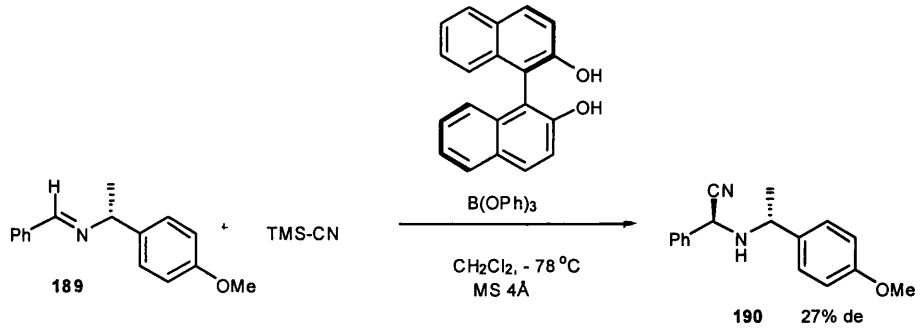
Following on from our theme of carbon-carbon bond forming reaction of imines it was decided to investigate the use of the boron-BINOL catalyst for asymmetric Strecker reactions, involving the addition of cyanide ion to imines. We carried out the reaction between benzylidenebenzylamine **42** and TMS-CN in dichloromethane at – 78 °C, mediated by the chiral boron-BINOL reagent, which was formed *in-situ* from mixing one equivalent of triphenyl borate with two equivalents of BINOL (Scheme 141).



Scheme 141: Strecker synthesis mediated by a BINOL-boron Lewis acid.

This reaction proceeded in 63% yield, to afford an α-amino nitrile. The product afforded is believed to be racemic given that no optical rotation was observed when compared with the specific rotation of $[\alpha]_d^{25}$ = -75 ° for the (*S*)-enantiomer.[132] To this

end it was decided to carry out a similar Strecker reaction using a chiral imine substrate to investigate whether the diastereoselectivity of the Strecker reaction could be improved using a boron-BINOL catalyst (Scheme 142).

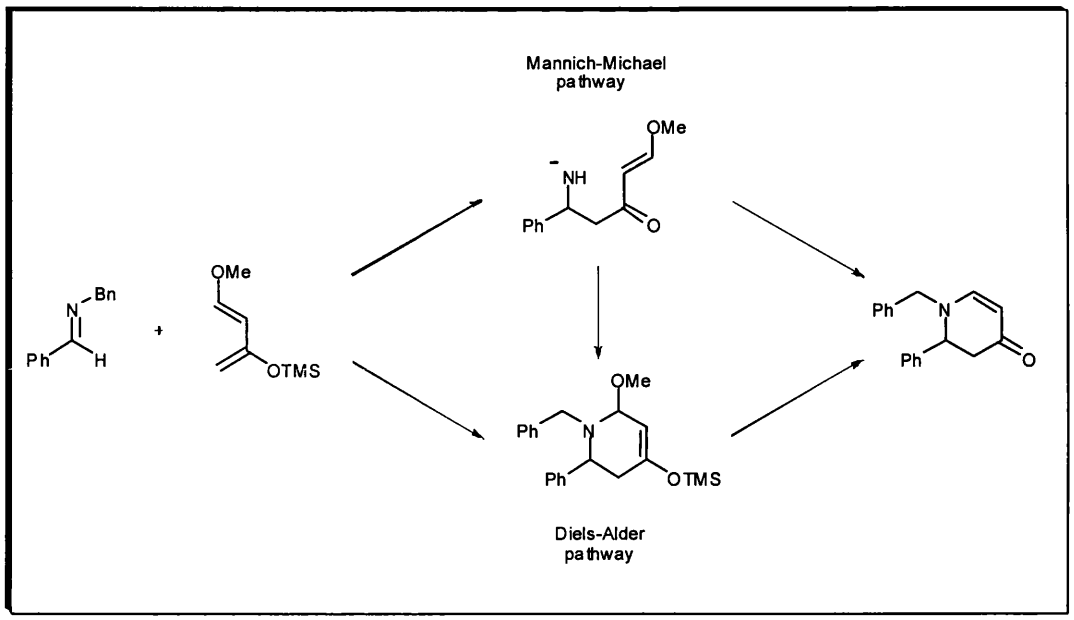


Scheme 142: Strecker synthesis between chiral imine and TMS-CN.

The reaction of enantiopure imine **189** with TMS-CN using the (*S*)-BINOL-boron complex yielded α-amino-nitrile compound **190** with rather poor 27% de. The same reaction using (*R*)-BINOL to generate the boron complex gave 20% de. In both cases the major diastereomer was shown to be (*S*,*R*)-**190** (Scheme 142) by comparison of its ^{1}H NMR spectrum with the literature.[133] Compound **190** could readily be turned into a desirable α-amino acid under acidic hydrolysis conditions, however given the low level of stereoselectivity attained, this was not carried out.

5.2.2 Mannich-type Reactions

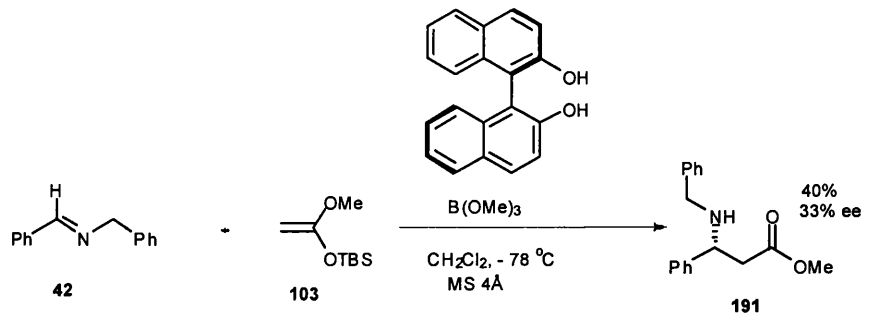
As discussed, the standard aza Diels-Alder reaction is believed to proceed by one of two mechanistic pathways, involving either a standard concerted "formal" [4+2] Diels-Alder pathway, or a stepwise reaction involving a Mannich-Michael reaction (Scheme 143).[30]



Scheme 143: The two different reaction pathways for the aza Diels-Alder reaction of activated dienes.

We believed that the aza Diels-Alder reaction carried out using Danishefsky's diene and aldimines mediated by the BINOL-boron Lewis acid was likely to be proceeding via a stepwise mechanism, which led us to attempt a Mannich-type reaction using a silyl ketene acetal as a nucleophile that effectively forms the first step of the stepwise aza Diels-Alder reaction.

The Mannich-type reaction we carried out used the aldimine benzylidenebenzylamine **42** which was reacted with silyl ketene acetal **103** to form β-amino-ester **191** (Scheme 144).



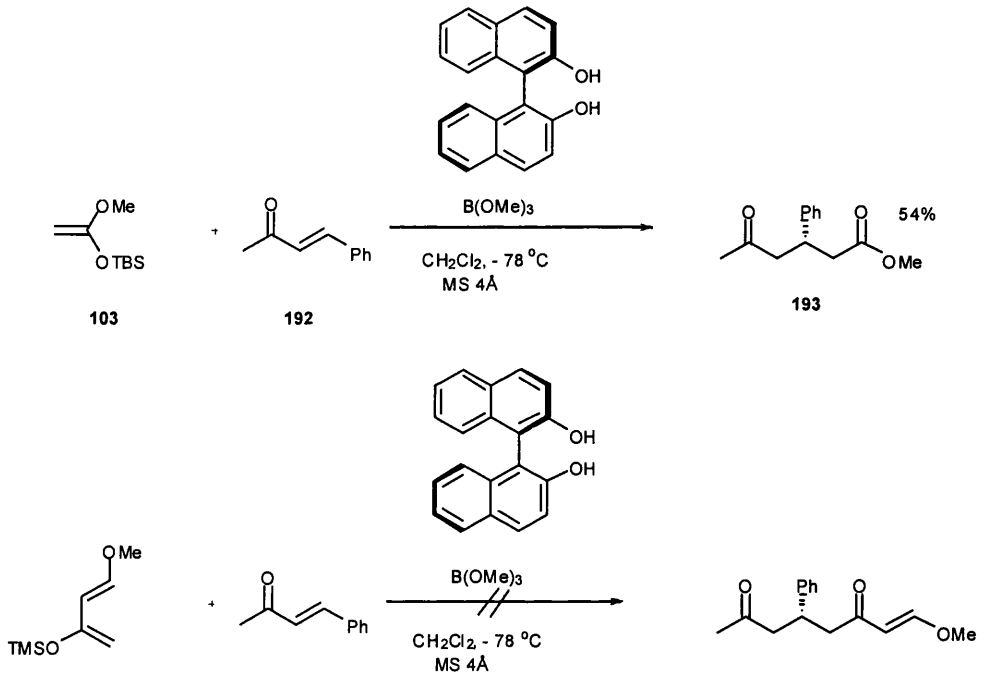
Scheme 144: Mannich reaction of silyl ketene acetal with aldimine.

This reaction was carried out in the usual manner using a chiral boron-BINOL reagent to give the desired β-amino-ester in modest yield and in a 32% ee determined by chiral

HPLC and comparison of the specific rotation with literature values.[113,122] Work is currently ongoing within the SDB group to optimise the stereocontrol of this potentially useful transformation.

5.2.3 Conjugate addition reactions mediated by the boron-BINOL Lewis acid

The conjugate addition reaction of silyl ketene acetals to α,β-unsaturated methyl ketones was also undertaken using our boron-BINOL catalysts. First we used Danishefsky's diene as a nucleophile, however no reaction took place. The use of the more reactive silyl ketene acetal **103** reacted with ketone **192** to yield the desired keto-ester **193** using a boron-BINOL Lewis acid (Scheme 145).



Scheme 145: Reactions of α,β-unsaturated ketones with silyl ketene acetal mediated by a boron-BINOL Lewis acid.

The formation of **193** proceeded in moderate yield of 54% although the enantiopurity is is believed to be very low when comparing our $[\alpha]_D^{25} = -3.04$ with the literature value of $[\alpha]_D^{25} = -22.4$ for the (*S*)-enantiomer.[134] We believe that silyl ketene acetal **103** must be more reactive towards ketone **192** than Danishefsky's diene given that no reaction occurs with the latter reagent.

5.3 Chapter summary

In this chapter we have demonstrated how boron-BINOL catalysts can be used in the aza Diels-Alder reaction with a range of substrates. In particular, imines formed from 2-naphthylbenzaldehyde and 3-pyridylcarboxaldehyde gave the greatest level of enantioselectivity as well as imines derived from benzaldehyde and allylamine. Others derived from straight chain aliphatic amines and ones containing primary alcohols were less successful using this class of catalyst.

The use of a three component aza Diels-Alder reaction has been optimised which allows for a one step dihydropyridone formation, allowing for rapid screening investigation and shorter natural product synthesis. In general the level of asymmetric induction remained the same for the stepwise boron-BINOL catalysed aza Diels-Alder reaction, however in some cases the yield of chiral dihydropyridone was slightly reduced.

The inverse addition methodology, first described in the previous chapter has shown promise with an increased enantioselectivity at room temperature for the 3-pyridyl pyridone **169**, which achieved an ee of 72 % using this technique. Also the propeller boronate **117** has been applied as a successful catalyst for the aza Diels-Alder reaction. At room temperature this species was used with a range of aza Diels-Alder substrates and resulted in higher levels of enantioselectivity when compared to Yamamoto's boron-BINOL catalyst. The same propeller boronate could also be used with a variety of Diels-Alder adducts at – 78 °C with similar or higher levels of enantioselectivity.

Finally, investigation of other reactions by the boron-BINOL catalyst has shown that Mannich, Strecker, and Michael additions are all possible. Initial results suggest that no asymmetric induction occur with the Strecker reactions, whilst asymmetric Mannich and conjugate addition reactions of silyl ketene acetal proceed in only moderate ee. These reactions and other carbon –carbon bond forming reactions are currently under further investigation within our research group.

6 Results and Discussion 5: Synthesis of Lythraceae Alkaloids

6.1 Lythraceae Alkaloids

Alkaloids from the Lythracea family of plants have been known and used in medicine since the early 1600's. Isolation of the first crystalline compounds by Ferris *et al.* in 1962 resulted in extensive structural studies that resulted in recognition of over twenty further alkaloids.[135] These alkaloids were isolated from the leaves of the *Lagerstroemia Subcostata* Koehne, which are widely distributed in the Amani islands of Taiwan and China. The pharmacological properties of these alkaloids are not fully known, however some of their properties have been clinically studied and they show a wide range of activity including anti-inflammatory, sedative, tranquilizer and diuretic effects. These Lythraceae alkaloids are based on a quinolizidine chemical structure, and they have attracted significant interest among organic chemists for the validation of new methodologies for alkaloid synthesis.[136-145] These 4-arylquinolizidine based Lythraceae alkaloids can exist as alcohols, as for the case with Lasubine (I), in an ester form as with Subcosine (II), or as macrocyclic lactones such as for Vertaline and Nesodine (Figure 49).

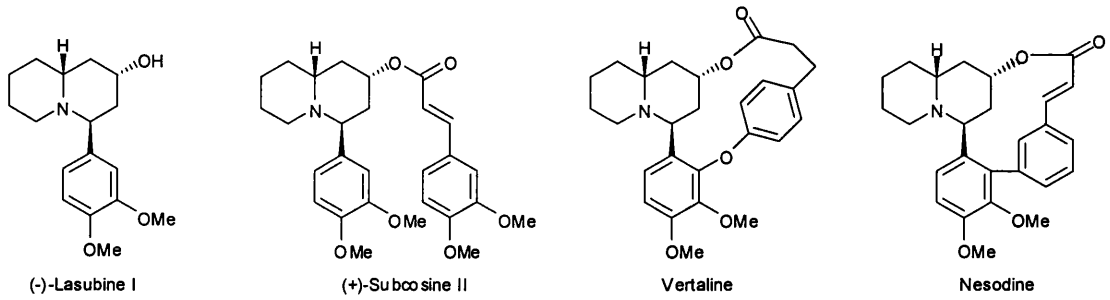


Figure 49: Various Lythraceae alkaloids.

In the previous chapters, investigations into the boron-BINOL catalysed asymmetric aza Diels-Alder reaction have been described. It was decided that to investigate the application of this boron-BINOL catalysed aza Diels-Alder reaction to a chiral natural

product synthesis, targeting the quinolizidine template of these Lythraceae alkaloids. Consequently, this chapter now describes my attempts directed towards the asymmetric synthesis of Lasubine (I) and Lasubine (II).

6.2 Literature Review

A range of different approaches for the asymmetric syntheses of the quinolizidine ring system have been carried out using a variety of strategies for ring formation. In general, the majority of the procedures employed, have been directed towards the synthesis of Lasubine (II) as the major diastereomer, employing methodology that includes the use of acylpyridinium salts, conjugate addition – cyclisations, ring closing metathesis and aza Diels-Alder reactions. In order to set the scene for my synthetic studies, a brief literature review now follows describing some of these previous approaches.

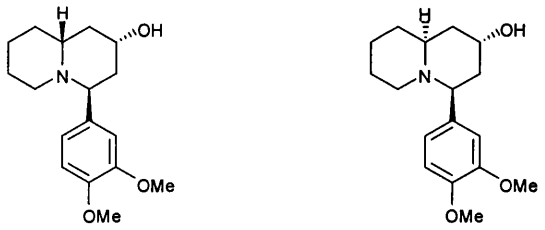
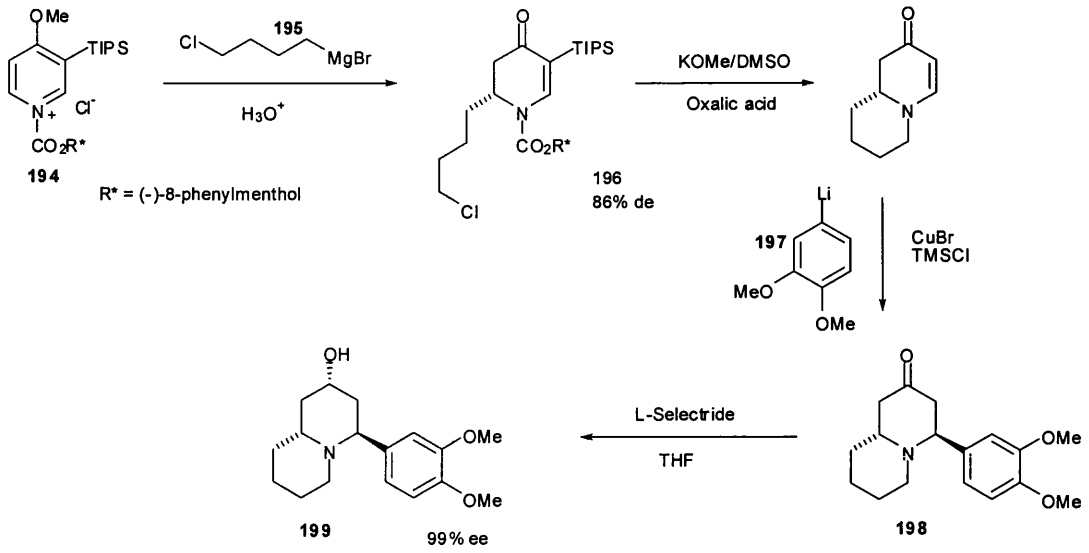


Figure 50: The structure of the Lythraceae alkaloids Lasubine I and Lasubine II.

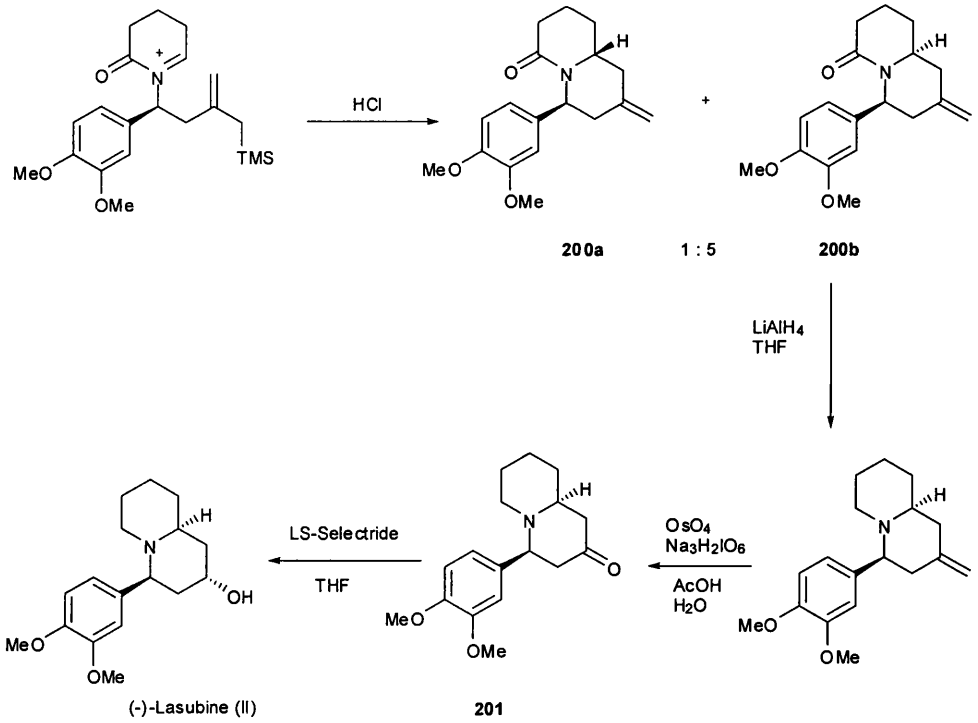
6.2.1 Synthesis of Lasubine from acylpyridinium salts

Comins *et al.* reacted *N*-acylpyridinium **194** with the Grignard reagent **195**,[146] using a (-)-8-phenylmenthol for stereocontrol, which gave dihydropyridone **196**. Removal of the *N*-acyl chiral auxiliary fragment, followed by intramolecular *N*-alkylation resulted in formation of the quinolizidine ring system. Next, conjugate addition of the aryl lithium **197** in the presence of copper bromide and chlorotrimethylsilane resulted in the pyridone **198** in 99% ee and 80% de. Finally the stereoselective reduction of the ketone functionality using L-Selectride gave the desired product **199**, (-)-Lasubine (I) in a total of five steps (Scheme 146).



Scheme 146: Synthesis of (-)-Lasubine I

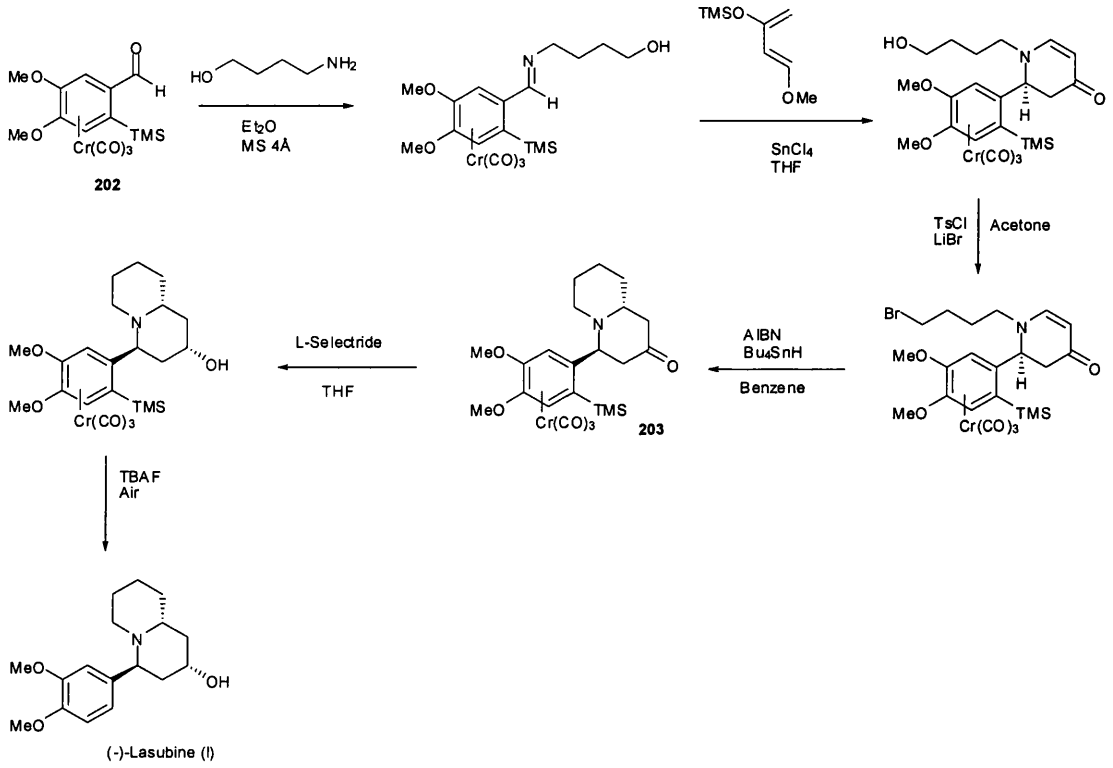
Remuson *et al.* prepared an *N*-acyl pyridinium salt **194** from a chiral starting material in five steps,[147] which was treated with HCl to afford a 1:5 mixture of quinolizidinone diastereomers **200a** and **200b**. Addition of lithium aluminium hydride reduced out the carbonyl of the lactam, followed by osmium tetroxide catalysed periodinane oxidation of the olefin to afford the desired quinolizidin-2-one **201**. Reduction with LS-Selectride formed the desired Lasubine (II) in a 14% overall yield and high enantioselectivity (>80% ee determined from $[\alpha]_D$) (Scheme 147).



Scheme 147: Synthesis of Lasubine (II) in 14% overall yield.

6.2.2 Synthesis of Lasubine employing the aza Diels-Alder reaction

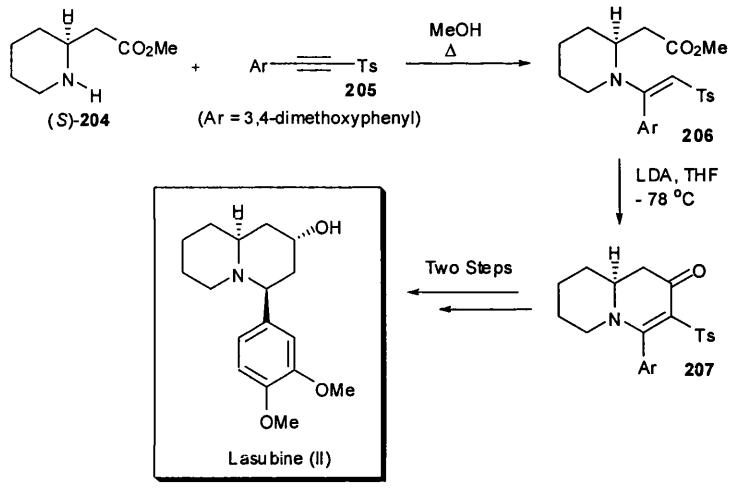
Kundig and co-workers have synthesised (-)-Lasubine (I) utilizing a diastereomerically pure chiral arylaldehyde tricarbonylchromium complex **202** for a highly diastereoselective aza Diels-Alder reaction, followed by an intramolecular radical cyclisation reaction to form the quinolizidinone intermediate **203** with a 9:1 trans selectivity. This intermediate was then reduced using L-Selectride, affording the desired (-)-Lasubine (I) in 98% ee (Scheme 148).[41]



Scheme 148: Synthesis of (-)-Lasubine I using an aryl chromium complex for diastereoselective control.

6.2.3 Synthesis of Lasubine employing conjugate addition reactions

Back *et al.* described an effective synthesis of Lasubine (II) employing a conjugate addition of amino ester (*S*)-**204** to the acetylenic sulfone **205** by refluxing in methanol for 4 h. The resultant enamine then underwent ring closure via α-deprotonation of **206** with LDA to afford enaminone **207** in 53% overall yield. Two further steps involving desulfonylation and carbonyl reduction afforded Lasubine II in 58% yield (Scheme 149).[148]



Scheme 149: Synthesis of Lasubine (II) employing conjugate addition to an acetylenic sulfone.

Ma *et al.* described a four step synthesis of (-)-Lasubine (II) employing a two component coupling of enantiopure β-amino ester **208** and iodide **209**.[141] Three subsequent nucleophilic attacks occurred, first the amino group of **208** attacked the terminal carbon of iodide **209**, to form the secondary amine, which attacks the electron deficient triple bond to provide the heterocyclic intermediate. The vinylogous anion generated in the conjugate addition step then attacked the carbonyl of β-amino ester **208** to form the bicyclic product **210** (Figure 51).

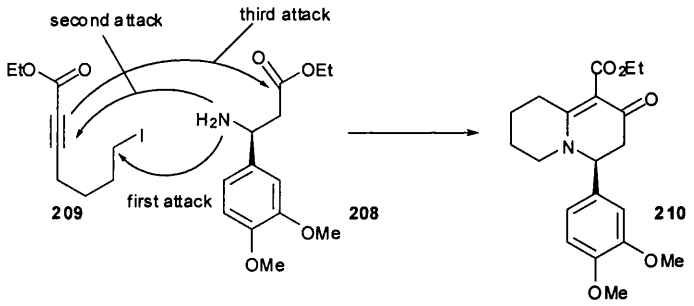
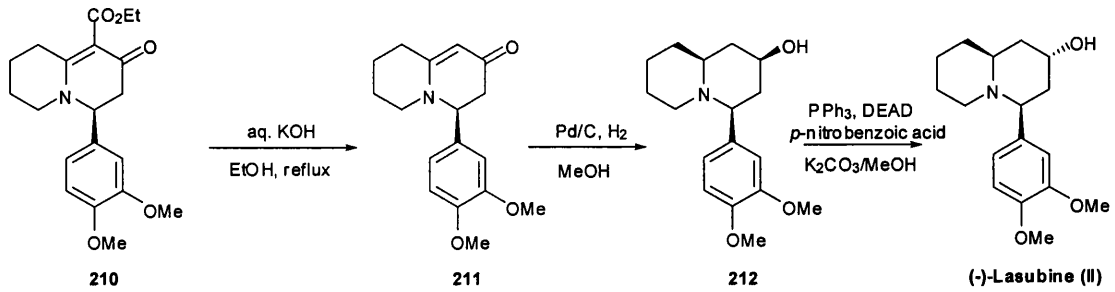


Figure 51: Two component coupling.

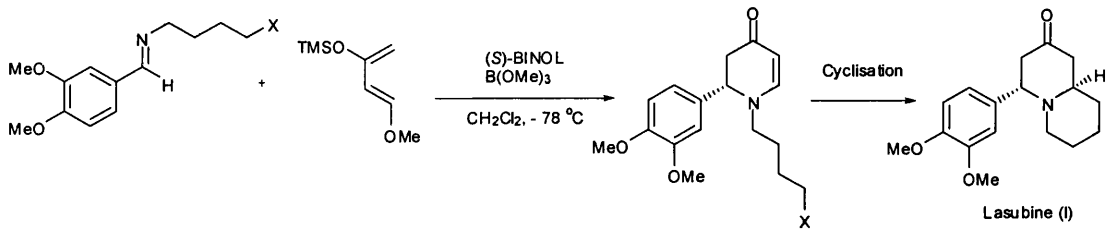
Quinolizidine **210** was then treated with potassium hydroxide, resulting in ester hydrolysis and decarboxylation affording enone **211** in 66% yield. Hydrogenation of **211** then resulted in alcohol **212**, which was subjected to Mitsunobu inversion to afford (-)-Lasubine (II) in 36% overall yield (Scheme 150).



Scheme 150: Synthesis of Lasubine (II).

6.3 Racemic Synthesis of Lasubine (I)

It was decided that Lasubine (I) represented a suitable target for a natural product synthesis employing the boron-BINOL mediated aza Diels-Alder reaction. The quinolizidine core could be formed by first preparing the required dihydropyridone via an aza Diels-Alder reaction, followed by addition of a second six-membered ring using either an ionic or radical intramolecular conjugate addition strategy (Scheme 151).

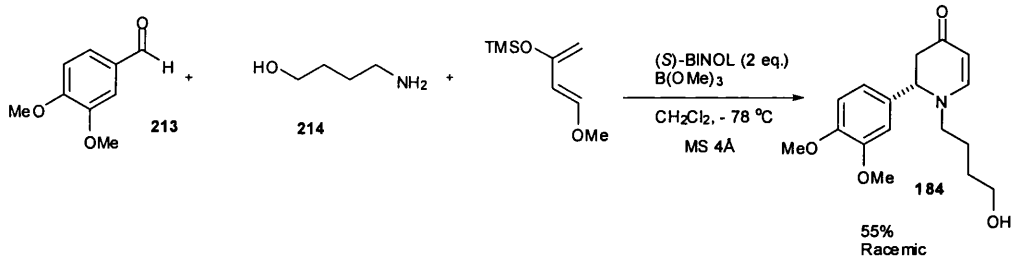


Scheme 151: Possible synthetic route to Lasubine (I).

The quinolizidinone formed could then be reduced with L-Selectride affording Lasubine (I). This strategy was similar to that described by Kundig *et al.* who employed an aza Diels-Alder reaction using an air-sensitive tricarbonylchromium complex, to prepare Lasubine (I) in high enantioselectivity.[41] A similar synthetic strategy employing my boron-BINOL catalyst to introduce stereocontrol into an aza Diels-Alder reaction could potentially result in formation of Lasubine (I) in four synthetic steps, compared with the seven steps previously required using the Kundig preparation.

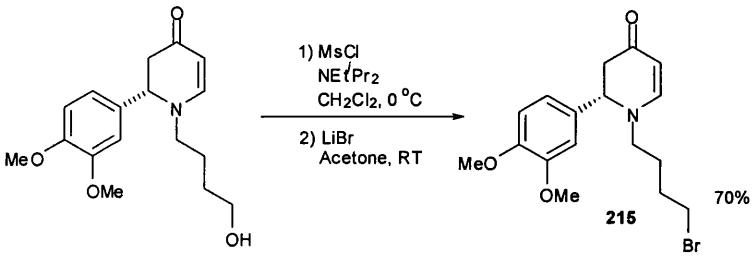
The first step of our synthesis of Lasubine (I) involved the one pot three component synthesis of dihydropyridone **184**. It has been described in the previous chapter how the boron-BINOL catalysed aza Diels-Alder reaction could be successfully carried out

using a three-component coupling method. Therefore, reaction of aldehyde **213** and amine **214**, and Danishefsky's diene resulted in formation of dihydropyridone **184** in 55% yield (Scheme 152). Unfortunately, it was found that no asymmetric induction had occurred in this aza Diels-Alder reaction, with pyridone **184** having been formed in essentially racemic form as determined by HPLC analysis. It was reasoned that the presence of a three hydroxyl group of amine **214** might have resulted in inefficient self-assembly of the chiral boron catalyst in these reactions. Therefore, the corresponding *O*-silylamine derivative was employed for synthesis, however once again only racemic pyridone **184** was recovered. It was decided to continue with the synthesis of Lasubine (I) using racemic pyridone **184**, since we required a racemic form of the natural product for comparison with any asymmetric preparation of Lasubine (I).



Scheme 152: Synthesis of pyridone **184** employing a one pot three component aza Diels-Alder reaction.

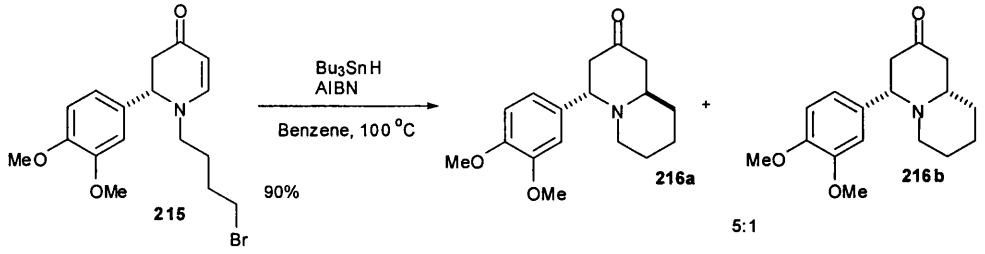
The next synthetic step involved conversion of the alcohol functionality of racemic **184** to the corresponding bromide **215**, involving treatment of **184** with mesyl chloride and Hunigs base to afford mesylate, that was then treated with lithium bromide to afford the desired ω-bromo-pyridone **215** in 70% yield (Scheme 153).



Scheme 153: Conversion of alcohol **184** to bromide **215**.

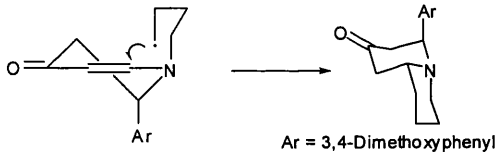
Bromide **215** was then employed for an intramolecular diastereoselective radical cyclisation reaction using tributyl tin hydride and the radical initiator AIBN at 100 °C in

benzene for 2 h which afforded a 5:1 mixture of the diastereoselective quinolizidinone **216a** and **216b** which were seperated by chromatography.



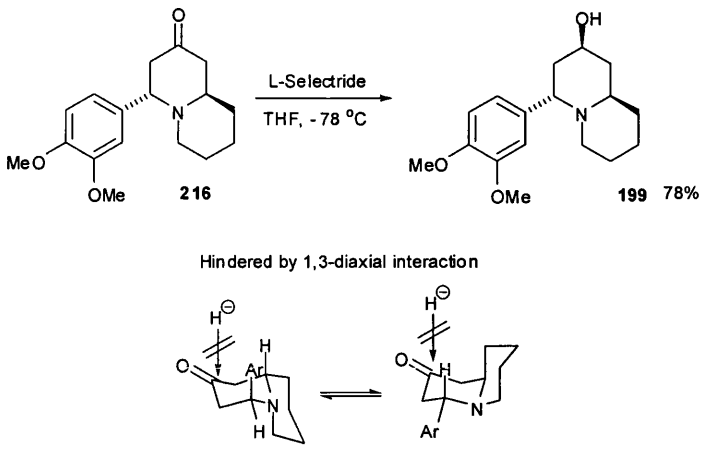
Scheme 154: Synthesis of quinolizidinones **216a** and **216b** via a radical cyclisation reaction.

The *trans* selectivity observed for the formation of the major *anti*-diastereoisomer **216a** could be justified by the fact that **215** adopts a half-boat conformation with its aryl substituent occupying a pseudo-axial environment. This results in the ω-radical undergoing intramolecular conjugate attack via an axial trajectory to afford the observed major diastereoisomer, with a *cis*-decaline like ring system. This product proved difficult to purify due to tin residues contaminating the product, however they were eventually removed by dissolving quinolizidinone **216** in acetonitrile and washing repeatedly with petroleum ether, with the tin residues being extracted into the petroleum ether layer.



Scheme 155: Radical addition via an axial trajectory.

The final stage of the synthesis involved reduction of the carbonyl functionality of the quinolizidinone **216** using the bulky reducing agent L-Selectride, which resulted in equatorial attack of hydride to form the desired axial hydroxyl functionality and the desired product Lasubine (I) in 78% yield.

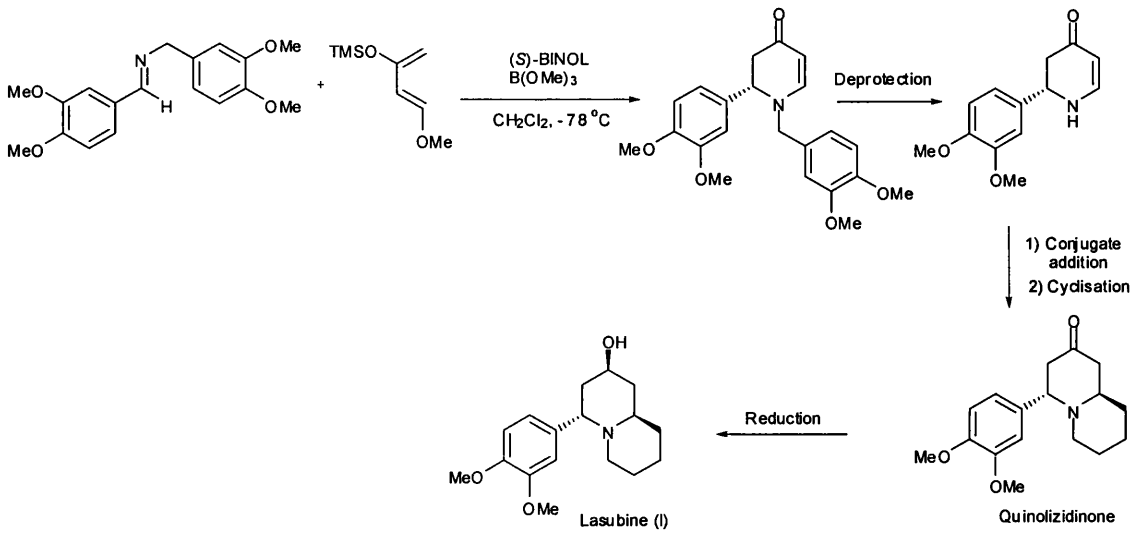


Scheme 156: Selective reduction to afford Lasubine (I) in 78% yield.

Racemic Lasubine (I) had therefore been synthesised in 23% overall yield in four steps, with the structure of the natural product being confirmed by comparison of its ^{1}H and ^{13}C NMR spectrum with those described in the literature. However the fact that no asymmetric induction has been observed in the initial boron-BINOL mediated aza Diels-Alder reaction meant that a new approach for its asymmetric synthesis was required.

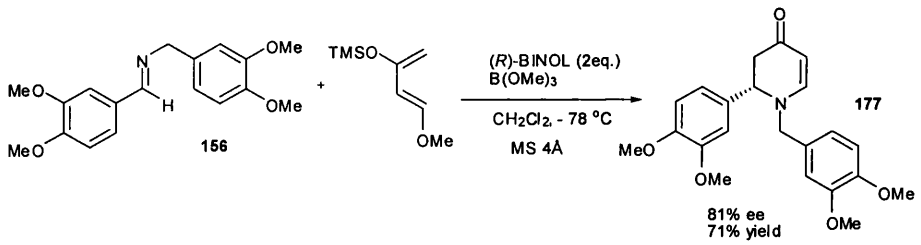
6.4 Asymmetric Synthesis of Lasubine (I) and Lasubine (II)

In the previous chapter a substrate screen of different imines in the boron-BINOL mediated aza Diels-Alder reaction had revealed what classes of dihydropyridones could be obtained in high ee.. Of particular interest was dihydropyridone **177**, that had been obtained in 81% ee and 73% yield. Oxidative removal of the *N*-benzyl group of this dihydropyridone, followed by intramolecular conjugate addition would allow for a possible synthetic route to the quinolizidine core (Scheme 157).



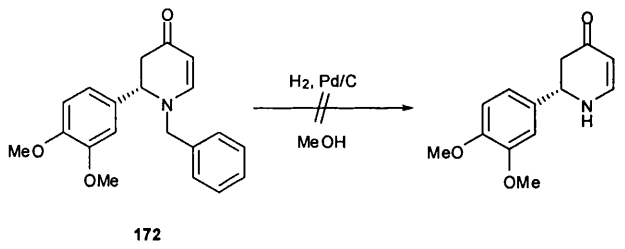
Scheme 157: Proposed synthetic route for the synthesis of Lasubine (I).

The first step of this synthesis involved a one pot three component aza Diels-Alder reaction affording the desired dihydropyridone **177** in 55% yield and 81% ee, however a higher yield was obtained when the imine **156** was preformed and employed for synthesis. This imine **156** was therefore employed in the asymmetric aza Diels-Alder reaction affording the desired dihydropyridone **177** in 71% yield and 81% ee (Scheme 158).



Scheme 158: Asymmetric aza Diels-Alder reaction of pyridone **177**.

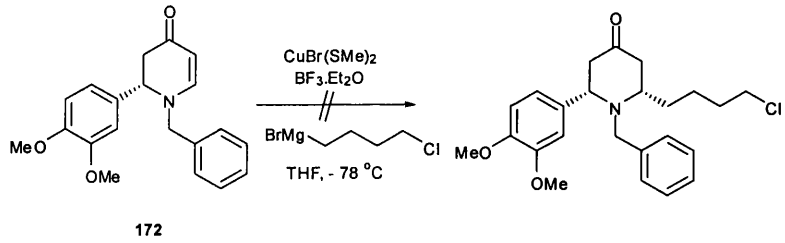
Following the successful synthesis of pyridone **177** we attempted to remove the *N*-benzyl group under oxidative conditions using ceric ammonium nitrate (CAN) and dichlorodicyanoquinone (DDQ). Unfortunately none of these methods were successful with only starting materials recovered. Hydrogenation was also attempted on *N*-benzyl pyridone **172**, which was obtained in 80% ee and 55% yield, but this also failed affording recovered starting material as the only product (Scheme 159).



172

Scheme 159: Attempted hydrogenation of pyridone **172**.

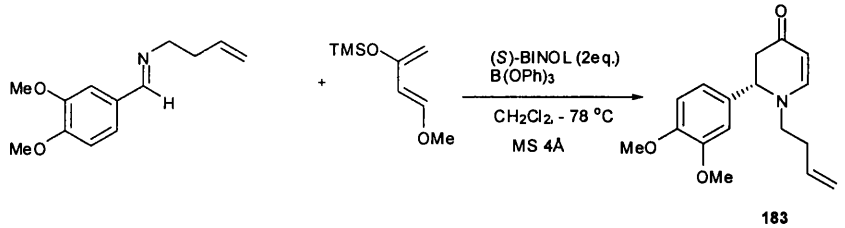
It was decided that debenzylation of **172** was likely to have failed due to of the enamide like character of the dihydropyridone substrates, therefore it was decided that intermolecular addition of a Gringard reagent to the enone system might allow for subsequent debenzylation at nitrogen. Grignard reagent **195** was prepared using a procedure previously described by Comins *et al.* who had previously added this reagent to a similar dihydropyridone,[146] however no evidence of the desired pyridone being formed was revealed by ^{1}H NMR analysis of the crude reaction product



172

Scheme 160: Attempted conjugate addition to pyridone **172**.

Following this unexpected result we considered the use of *N*-butenyl pyridone **183**, that had the potential to undergo a similar conjugate addition reaction described in scheme Scheme 160. It was proposed that, the alkene functionality of **183** could be converted to its corresponding bromide via hydroboration and substitution of the resultant alcohol with bromide anion that could then be used as a substrate for an intramolecular conjugate addition reaction. Much to our surprise it was found that dihydropyridone **183** was formed as a racemic mixture using our boron-BINOL catalyst in poor yield making this pyridone unsuitable as a basis for the asymmetric synthesis of Lasubine (I).

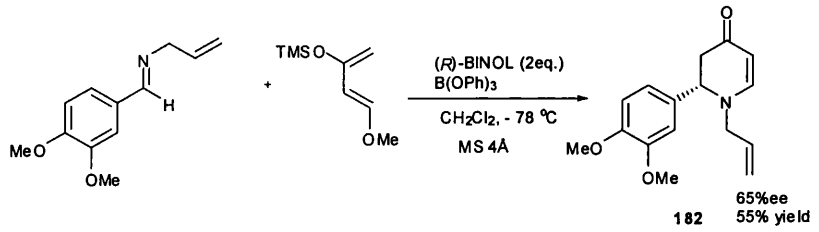


183

Scheme 161: Synthesis of *N*-butenyl pyridone **183** in poor yield.

It had been shown that *N*-allyl pyridone **181** could be synthesised in 77% ee using triphenyl borate to prepare the boron-BINOL catalyst. It was proposed that an *N*-allyl derived pyridone could be employed for an asymmetric synthesis of Lasubine that would allow the quinolizidinone skeleton to be prepared using a ring closing metathesis reaction.[140]

Therefore, dihydropyridone **182** containing an *N*-allyl group and a 3,4-dimethoxy phenyl group was chosen as a key synthon for the asymmetric synthesis of Lasubine (I). Therefore, *N*-allyl imine **163** was reacted with Danishefsky's diene **25** at -78 °C in 65% ee and in 55% yield. Unfortunately, repeated fractional recrystallisation resulted in no increase in ee occurring (Scheme 162).



Scheme 162: Boron-BINOL catalysed aza Diels-Alder reaction to form pyridone **182**.

With a route to enantioenriched pyridone **182** in hand it was proposed that it could be subjected to a conjugate addition reaction using allyl cuprate, followed by a ring closing metathesis reaction to form the second ring of the quinolizidine structure (Figure 52).

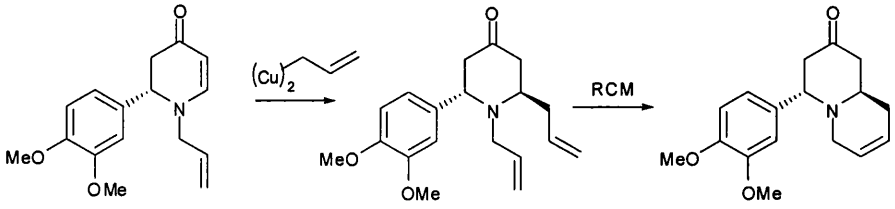
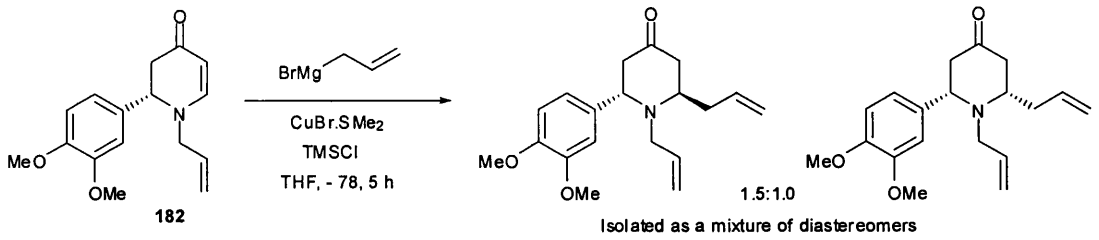


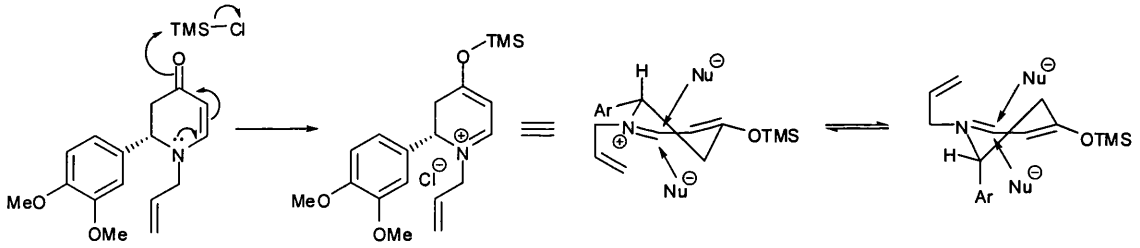
Figure 52: Pyridones employed for the natural product synthesis of Lasubine (I)

Dihydropyridone **182** was subjected to a conjugate addition reaction using allylmagnesium bromide using copper bromide dimethylsulfide and chlorotrimethylsilane. This afforded the addition product **217** in 61% yield after column chromatography, as a mixture of diastereomers in a ratio of 1.5:1.0 (Scheme 163).



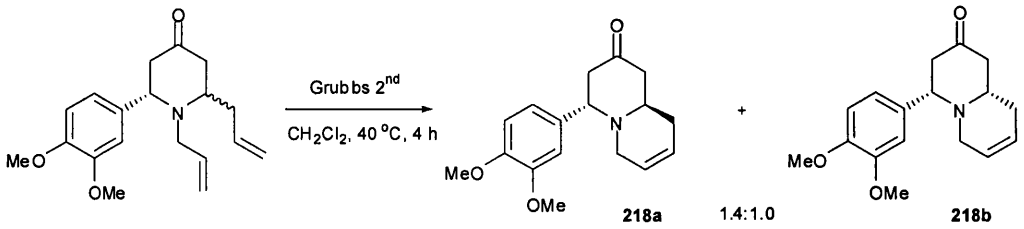
Scheme 163: Conjugate addition to pyridone **182**.

The diastereomeric ratio of this conjugate addition reaction was determined from the ^{13}C NMR spectra, however at this stage of the synthesis the conformation of the major diastereoisomer was unknown. However, subsequent synthetic elaboration (*vide supra*) enabled us to correlate the major diastereoisomer with Lasubine (I), and the minor diastereoisomer with Lasubine (II), and as a consequence their configurations were assigned accordingly. In similar conjugate addition reactions, high levels of diastereoselectivity had been achieved, however these examples had not required the use of TMSCl to activate the pyridone for addition.[149] It was proposed that the presence of TMSCl would allow for the dihydropyridone to form an iminium-silyl enol ether, which would exist in a planar conformer so that addition of allyl-cuprate to either the *Re* or *Si* faces would be equally favoured.



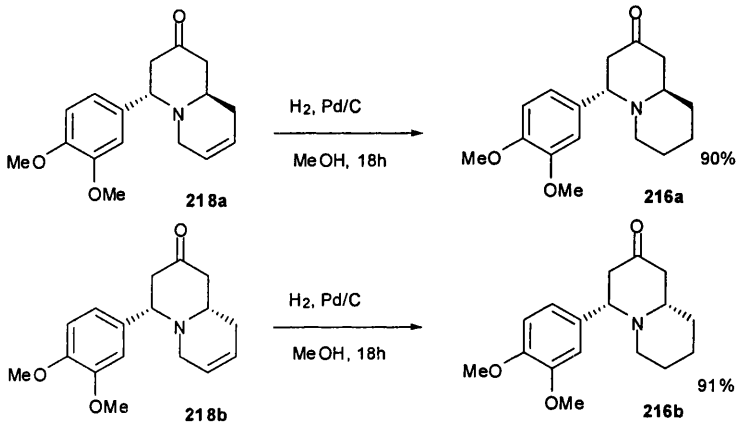
Scheme 164: Mechanism for the conjugate addition reaction.

The mixture of diastereoisomers were treated with 5 mol% of second generation Grubbs catalyst and refluxed in dichloromethane for 4 h, which afforded a 1.4:1.0 mixture of quinolizidinone diastereoisomers in 76% yield. These diastereomers were readily separated by column chromatography (1:1 EtOAc/hexane), to afford **218a** and **218b** in 44% and 33% yield respectively (Scheme 165).



Scheme 165: Ring closing metathesis reaction to form quinolizidinones **218a** and **218b**.

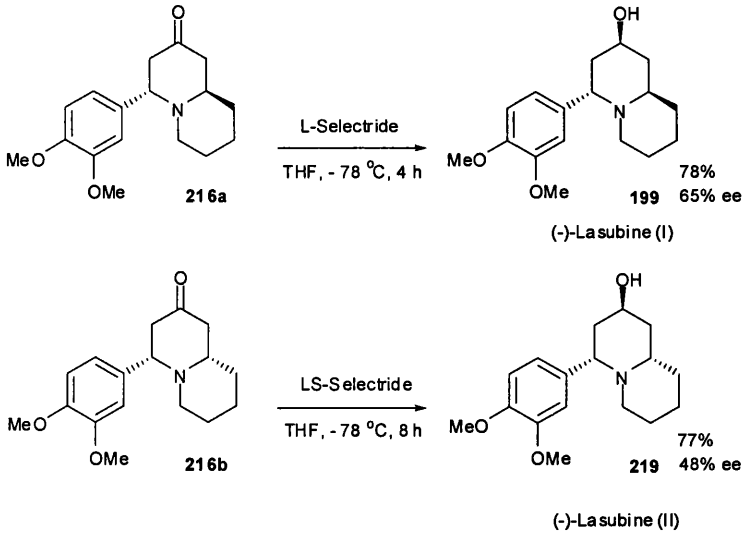
Both **218a** and **218b** were separately treated with H_2 and Pd/C and were successfully hydrogenated to afford the desired quinolizidinones **216a** and **216b** in 90% and 91% yield respectively (Scheme 166).



Scheme 166: Hydrogenation of **218a** and **218b**.

The final stage of the synthesis was to selectively reduce the carbonyl of the quinolizidinone to the corresponding alcohol using L-Selectride for the anti diastereomer affording (-)-Lasubine (I) in 10% overall yield and in six steps. The $[\alpha]_D^{25}$ of – 4 ° corresponded to a 50% ee when compared to the literature value for the natural product of $[\alpha]_D^{25}$ – 7 °,[147] whilst reaction with enantiopure Moshers acid chloride and analysis of the resultant esters by ^1H NMR spectroscopy revealed an 65% ee, this was the same level of enantioselectivity obtained for the parent dihydropyridone **182**. Similarly LS-Selectride was used to reduce the syn diastereomer following literature precedent. This afforded (-)-Lasubine (II) in 8% overall yield over six steps with an $[\alpha]_D^{25}$ of – 13 ° which corresponded to a 40% ee which compared to the literature value for the natural product of $[\alpha]_D^{25}$ – 35 °.[147] Once again reaction with Moshers acid chloride followed by ^1H NMR analysis of the resulatant esters revealed the enantioselectivity to be 48% ee by ^1H NMR spectroscopy (Scheme 167). Unfortunately,

the enantiopurity of Lasubine (I) and Lasubine (II) could not be increased by fractional recrystallisation as these natural products are oils.



Scheme 167: Final synthesis of Lasubine (I) and Lasubine (II).

6.5 Conclusions

In this chapter it has been described how the Lythraceae alkaloids Lasubine (I) and Lasubine (II) could be synthesised. Firstly, racemic Lasubine (I) was synthesised in a four step procedure using a non-stereoselective one pot three component aza Diels-Alder reaction, followed by a diastereoselective radical cyclisation reaction. An alternative stereoselective synthesis of Lasubine alkaloids were also developed employing the pyridone **182** as a key intermediate. Conjugate addition of an allyl cuprate reagent to this pyridone, followed by ring closing metathesis afforded a mixture quinolizidinone **218** diastereoisomers in a 1.4:1.0 ratio. These were separated then converted to enantioenriched Lasubine (I) and Lasubine (II) after two further synthetic steps.

7 Experimental

7.1 General procedures

^{1}H, ^{13}C and ^{11}B NMR spectra were recorded on a Brucker Avance AC-300 spectrometer at 300.22, 75.49 and 96.32 MHz respectively, or on a Brucker Avance WH-400 spectrometer at 399.78, 100.52 and 128.38 MHz respectively in $CDCl_3$, CD_2Cl_2 and acetone-d6, using tetramethylsilane and/or the residual solvent peak as the internal standard with $BF_3.Et_2O$ as the external standard for ^{11}B NMR spectroscopy. Chemical shifts (δ_H) are given in parts per million and coupling constants (J) are quoted to the nearest 0.1 Hz. The multiplicities and general assignments of spectroscopic data are denoted as follows: singlet (s), broad singlet (br s), doublet (d), doublet of doublets (dd), doublet of triplets (dt), doublet of doublet of triplets (ddt), broad doublet (br d), triplet (t), apparent triplet (app t), triplet of doublets (td), quartet (q), quintet (quin), heptuplet (hept), unresolved multiplet (m), and aromatic (Ar).

Infrared spectra were recorded on a Perkin Elmer 1600 series FT-IR spectrometer with internal background calibration for the range 600-4000 cm^{-1}, as solutions in chloroform ($CHCl_3$) and (CH_2Cl_2), using the compound neat (neat), or KBr discs (KBr) as stated. Selected absorptions were recorded in wavenumbers (cm^{-1}).

All capillary melting points were recorded using a Büchi 535 melting point apparatus. The readings were taken from a mercury-in-glass thermometer and were reported uncorrected as the meniscus point. Where the sample changed colour or evolved gas during or after the melt, thermal decomposition (dec) is noted.

Optical rotations were recorded on an Optical Activity Limited AA-10 automatic polarimeter with a path length of 1 dm. Concentrations (c) are quoted in g/100ml.

Mass spectra including high resolution spectra were recorded by the EPSRC national mass spectrometry service centre, Swansea, using electron impact (EI), chemical ionisation (CI) or electrospray (ES). A Micromass Quattro II triple quadrupole was

used for low resolution measurements using ammonia as the CI reagent gas. A MAT900 high resolution spectrometer was used for high resolution measurments.

High performance liquid chromatography was performed on either a TSP thermo separation products spectra series system or a Perkin Elmer series 200 high performance liquid chromatography system, using either a Chiralcel OD or OD-H columns or a Chiralpak AD column.

Crystallographic measurements were recorded on a Nonius KappaCCD diffractometer with Mo-Kα radiation (λ = 0.71074 Å). All structures were solved by direct methods and refined on all F_2 data using the SHELX-97 suite of programmes.

Thin layer chromatography was performed on Macherey-Nagel aluminum backed plates coated with a 0.20mm layer of silica 60 with a fluorescent indicator UV_{254}. Plates were visualised under ultra violet light (at 254 nm) or by staining with potassium permanganate, vanillin or phosphomolybdic acid before heating. Column chromatography was carried out using Merck Kieselgel 60H silica gel. Samples were added to the top of the column pre-absorbed onto silica.

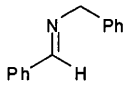
Dichloromethane, diethyl ether, tetrahydrofuran, acetonitrile and toluene were collected from an Innovative Technology Pure-Solv solvent purification system (SPS), alternatively tetrahydrofuran and diethyl ether were distilled from sodium benzophenone ketyl under nitrogen, whilst Dichloromethane was distilled from CaH_2 under nitrogen. Petrol refers to light petroleum, bp 40-60 °C and was distilled without drying.

All chemicals were used as supplied unless otherwise stated, and were supplied from Acros Organics, Alfa Aesar, Avocado, Fisher Scientific Europe, Fluka, Lancaster Synthesis, Sigma-Aldrich and Strem Chemicals.

7.2 General procedure for the preparation of imines used as dienophiles in the aza Diels-Alder reaction

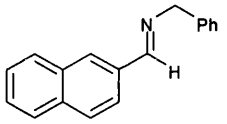
A solution of aldehyde (1 eq.) and amine (1 eq.) in THF were stirred in the presence of magnesium sulfate. After 5 hours the reaction mixture was filtered and the solvent removed *in vacuo* to afford the product without further purification unless otherwise stated.

N-Benzylidenebenzylamine 42[150]



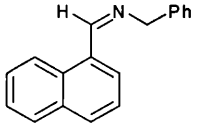
Yellow oil (100%), δ_H (300MHz, $CDCl_3$) 4.89 (2H, s, C*H*$_2$Ph), 7.26-7.55 (8H, m, Ar), 7.81-7.90 (2H, m, Ar), 8.44 (1H, s, C*H*N); δ_C (75MHz, $CDCl_3$) 65.5, 127.5, 128.4, 128.8, 129.0, 129.1, 131.3, 136.7, 139.8, 162.5.

N-(Naphthalen-2-ylmethylene)-1-phenylmethanamine 150[151]



White solid (60%), mp 84-86 °C (lit., 84-86 °C); δ_H (300MHz, $CDCl_3$) 4.89 (2H, s, C*H*$_2$Ph), 7.35-7.40 (5H, m, Ar*H*), 7.50-7.57 (2H, m, Ar*H*), 7.83-7.92 (3H, m, Ar*H*), 8.04-8.10 (2H, m, Ar*H*) 8.58 (1H, s, C*H*N); δ_C (75MHz, $CDCl_3$) 65.6, 124.4, 126.7, 127.4, 127.6, 128.3, 128.4, 128.9, 128.9, 130.5, 133.5, 134.3, 135.2, 139.7, 162.4; *m/z* (ES^+) 246.1276 ($[M+H]^+$ - $C_{18}H_{16}N$ requires 246.1277) (CI^+) 246.2 [M+H] (100%).

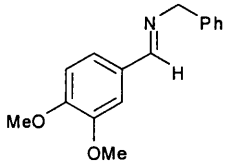
N-(Naphthalen-1-ylmethylene)-1-phenylmethanamine 151[152]



Yellow solid (95%), mp 189-191 °C (lit., 189 °C); δ_H (300MHz, $CDCl_3$) 4.89 (2H, s, C*H*$_2$Ph), 7.35-7.40 (5H, m, Ar*H*), 7.50-7.57 (2H, m, Ar*H*), 7.83-7.92 (3H, m, Ar*H*), 8.04-8.10 (2H, m, Ar*H*) 8.58 (1H, s, C*H*N); δ_C (75MHz, $CDCl_3$) 66.5, 124.8, 125.7,

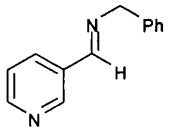
126.5, 127.4, 127.6, 128.4, 128.9, 129.1, 129.5, 131.6, 131.8, 132.0, 134.3, 139.9, 162.1; *m/z* (ES^+) 246.1276 ($[M+H]^+$ - $C_{18}H_{16}N$ requires 246.1277) (CI^+) 246.2 [M+H] (100%).

N-(3,4-Dimethoxybenzylidene)-1-phenylmethanamine 152[153]



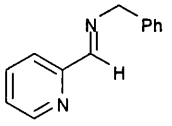
Trituration with MeOH afforded a yellow solid (95%), mp 55-57 °C; δ_H (300MHz, $CDCl_3$) 3.92 (3H, s, OC*H*$_3$), 3.94 (3H, s, OC*H*$_3$), 4.82 (2H, s, C*H*$_2$Ph), 6.86-6.92 (1H, m, Ar*H*), 7.17-7.39 (6H, m, Ar*H*), 7.50-7.52 (1H, m, Ar*H*), 8.31 (1H, s, C*H*N); δ_C (75MHz, $CDCl_3$) 56.3, 65.3, 109.2, 110.8, 123.8, 127.4, 128.4, 128.9, 129.8, 139.9, 149.7, 151.8, 162.0.

1-Phenyl-*N*-(pyridin-3-ylmethylene)methanamine 153[154]



Yellow oil (88%), δ_H (300MHz, $CDCl_3$) 4.77 (2H, s, C*H*$_2$Ph), 7.16-7.32 (6H, m, Ar*H*), 8.05-8.11 (1H, m, Ar*H*), 8.34 (1H, s, C*H*N), 8.54-8.59 (1H, m, Ar*H*), 8.81-8.83 (1H, m, Ar*H*); δ_C (75MHz, $CDCl_3$) 65.7, 124.1, 127.6, 128.4, 129.0, 132.1, 135.0, 139.2, 150.8, 152.0, 159.4; *m/z* (ES^+) 197.1072 ($[M+H]^+$ - $C_{13}H_{13}N_2$ requires 197.1073) (CI^+) 197.0 [M+H] (100%).

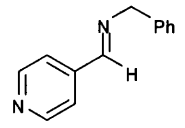
1-Phenyl-*N*-(pyridin-2-ylmethylene)methanamine 154[155]



Yellow oil (92%), δ_H (300MHz, $CDCl_3$) 4.66 (2H, s, C*H*$_2$Ph), 7.00-7.25 (6H, m, Ar*H*), 7.42-7.51 (1H, m, Ar*H*), 7.82-7.89 (1H, m, Ar*H*), 8.30 (1H, s, C*H*N), 8.40-8.45 (1H, m,

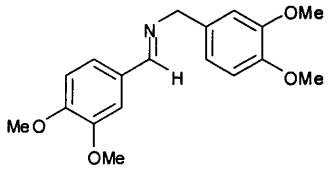
Ar*H*); δ_C (75MHz, $CDCl_3$) 65.3, 121.7, 125.211, 127.5, 128.6, 129.0, 136.9, 139.1, 149.8, 154.9, 163.2.

1-Phenyl-*N*-(pyridin-4-ylmethylene)methanamine 155[156]



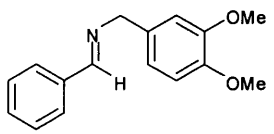
Yellow oil (90%), δ_H (300MHz, $CDCl_3$) 4.55 (2H, s, CH_2Ph), 6.93-7.20 (5H, m, Ar*H*), 7.28-7.40 (2H, m, Ar*H*), 8.02 (1H, s, C*H*N), 8.33-8.45 (2H, m, Ar*H*); δ_C (75MHz, $CDCl_3$) 65.4, 122.5, 127.7, 128.4, 129.0, 138.9, 143.3, 150.7, 160.3.

***N*-(3,4-Dimethoxybenzylidene)-1-(3,4-dimethoxyphenyl)methanamine 156[157]**



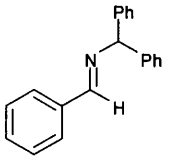
Trituration with MeOH afforded a cream solid (96%), mp 79-81 °C (lit., 77-79 °C); δ_H (300MHz, $CDCl_3$) 3.80 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 4.67 (2H, s, CH_2Ph), 6.71-6.82 (4H, m, Ar*H*), 7.06-7.13 (1H, m, Ar*H*), 7.36-7.40 (1H, m, Ar*H*), 8.20 (1H, s, C*H*N); δ_C (75MHz, $CDCl_3$) 54.3, 62.8, 106.9, 108.5, 109.3, 109.5, 118.3, 121.5, 127.5, 130.1, 146.2, 147.4, 149.5, 159.4.

***N*-Benzylidene-1-(3,4-dimethoxyphenyl)methanamine 157[24]**



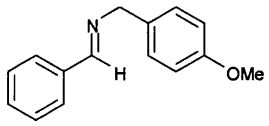
Yellow oil (99%), δ_H (300MHz, $CDCl_3$) 3.87 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 4.77 (2H, s, CH_2Ph), 6.82-6.91 (3H, m, Ar*H*), 7.38-7.45 (2H, m, Ar*H*), 7.74-7.81 (2H, m, Ar*H*), 8.37 (1H, s, C*H*N); δ_C (75MHz, $CDCl_3$) 56.4, 65.2, 111.8, 120.6, 128.7, 129.0, 132.3, 136.6, 148.5, 149.4, 162.1; *m/z* (CI^+) 256.0 [M+H] (100%).

_N_-Benzylidene-1,1-diphenylmethanamine 158[156]



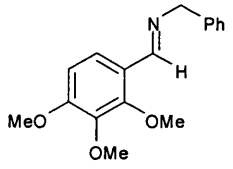
Yellow solid (90%), mp 97-99 °C (lit., 97 °C); δ_H (300MHz, $CDCl_3$) 5.53 (1H, s, C*H*Ph_2), 7.05-7.57 (13H, m, Ar*H*), 7.65-7.83 (2H, m, Ar*H*), 8.34 (1H, s, C*H*N); δ_C (75MHz, $CDCl_3$) 78.6, 127.6, 128.3, 129.1, 129.2, 131.4, 137.0, 144.5, 161.4.

_N_-Benzylidene-1-(4-methoxyphenyl)methanamine 159[158]



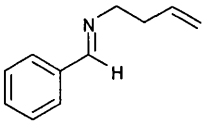
Yellow oil (67%), δ_H (300MHz, $CDCl_3$) 3.69 (3H, s, O*C*H_3), 4.67 (2H, s, CH_2Ph), 6.74-6.84 (2H, m, Ar*H*), 7.12-7.20 (2H, m, Ar*H*), 7.26-7.35 (3H, m, Ar*H*), 7.63-7.72 (2H, m, Ar*H*), 8.26 (1H, s, C*H*N); δ_C (75MHz, $CDCl_3$) 55.7, 64.9, 114.4, 128.7, 129.0, 129.6, 131.1, 136.6, 159.1, 162.1.

1-Phenyl-_N_-(2,3,4-trimethoxybenzylidene)methanamine 160



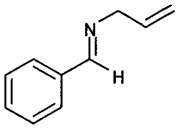
Yellow oil (99%), ν_{max}(neat)/cm^{-1} 1637 (C=N); δ_H (300MHz, $CDCl_3$) 3.81 (3H, s, O*C*H_3), 3.82 (3H, s, O*C*H_3), 3.87 (3H, s, O*C*H_3), 4.74 (2H, s, CH_2Ph), 6.62-6.66 (1H, m, Ar*H*), 7.16-7.28 (5H, m, Ar*H*), 7.66-7.70 (1H, m, Ar*H*), 8.59 (1H, s, C*H*N); δ_C (75MHz, $CDCl_3$) 55.0, 59.9, 60.9, 64.4, 106.4, 121.4, 121.7, 125.8, 126.9, 127.4, 138.7, 140.8, 152.9, 154.9, 156.5; *m/z* (ES^+) 286.1442 ($[M+H]^+$ - $C_{17}H_{20}O_3N$ requires 286.1438) (CI^+) 286.2 [M+H] (100%).

N-Benzylidenebut-3-en-1-amine 161[159]



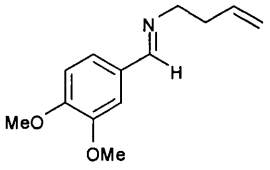
Yellow oil (85%), δ_H (300MHz, $CDCl_3$) 2.49 (2H, app q, J = 7.2 CH_2CH_2CH=), 3.70 (2H, t, J = 7.2, NCH_2CH_2), 5.05 (1H, dd, J = 10.2, 1.8 =CH^cH) 5.11 (1H, dd, J = 17.0, 1.8 =CH^tH), 5.87 (1H, ddt, J = 17.0, 10.2, 7.2, CH_2=CH), 7.37-7.45 (3H, m, Ar*H*), 7.70-7.79 (2H, m, Ar*H*), 8.27 (1H, s, C*H*N); δ_C (75MHz, $CDCl_3$) 35.6, 61.4, 116.6, 128.5, 129.0, 129.4, 131.0, 136.6, 161.8.

N-Benzylideneprop-2-en-1-amine 44[160]



Yellow oil (95%), δ_H (300MHz, $CDCl_3$) 4.25 (2H, d, J = 5.7, CH_2CH=), 5.16 (1H, dd, J = 10.2, 1.5, =CH^cH), 5.24 (1H, dd, J = 17.3, 1.5 =CH^tH), 6.07 (1H, ddt, J = 17.3, 10.2, 5.7, CH_2=CH), 7.29-7.45 (3H, m, Ar*H*), 7.70-7.80 (3H, m, Ar*H*), 8.26 (1H, s, C*H*N); δ_C (75MHz, $CDCl_3$) 35.7, 56.4, 61.4, 109.1, 110.8, 116.5, 123.4, 128.7, 136.7, 149.7, 151.7, 161.2; *m/z* (EI) 220.1332 ($[M+H]^+$ - $C_{13}H_{18}NO_2$ requires 220.1332) (CI^+) 220.1 [M+H] (100%).

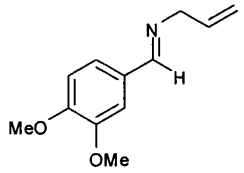
N-(3,4-Dimethoxybenzylidene)but-3-en-1-amine 162



Yellow oil (65%), ν_{max}(neat)/cm^{-1} 1643 (C=N); δ_H (300MHz, $CDCl_3$) 2.38 (2H, app q, J = 7.2, CH_2CH_2CH=), 3.57 (2H, t, J = 7.2, NCH_2CH_2), 3.83 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 4.96 (1H, dd, J = 10.5, 1.5 =CH^cH) 5.02 (1H, dd, J = 17.3, 1.5 =CH^tH), 6.07 (1H, ddt, J = 17.3, 10.5, 7.2, CH_2=CH), 6.77-6.82 (1H, m, Ar*H*), 7.04-7.09 (1H, m, Ar*H*), 7.28 (1H, s, Ar*H*), 8.10 (1H, s, C*H*N); δ_C (75MHz, $CDCl_3$) 63.9, 116.5, 128.3,

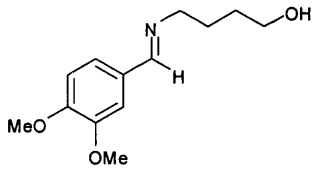
128.6, 129.0, 131.1, 136.3, 162.4; *m/z* (EI) 144.0808 ($[M-H]^+$ - $C_{10}H_{10}N$ requires 144.0808) (CI^+) 146.1 [M+H] (100%).

_N_-(3,4-Dimethoxybenzylidene)prop-2-en-1-amine 163



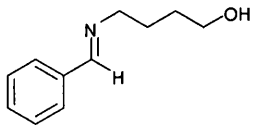
Yellow oil (99%), ν_{max}(neat)/cm^{-1} 1647 (C=N); δ_H (300MHz, $CDCl_3$) 3.87 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 4.20 (2H, d, J = 5.7, CH_2CH=), 5.08-5.26 (2H, m, CH=CH_2), 6.07 (1H, ddt, J = 16.9, 10.2, 5.7, CH_2=CH), 6.80-6.87 (1H, m, ArH), 7.09-7.15 (1H, m, ArH), 7.40-7.45 (1H, m, ArH), 8.16 (1H, s, CHN); δ_C (75MHz, $CDCl_3$) 56.2, 63.6, 109.0, 110.7, 116.2, 123.5, 130.4, 136.4, 149.6, 151.7, 161.9; *m/z* (ES^+) 206.1175 ($[M+H]^+$ - $C_{12}H_{16}N$ requires 206.1176) (CI^+) 206.1 [M+H] (100%).

4-(3,4-Dimethoxybenzylideneamino)butan-1-ol 164



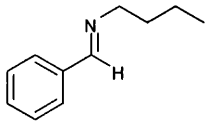
Yellow oil (98%), ν_{max}(neat)/cm^{-1} 1644(C=N), 3272 (OH); δ_H (300MHz, $CDCl_3$) 1.70-1.87 (4H, m, 2 x CH_2), 3.56-3.76 (4H, m, 2 x CH_2), 3.89 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 6.84-6.88 (1H, m, ArH), 7.11-7.16 (1H, m, ArH), 7.35-7.37 (1H, m, ArH), 8.17 (1H, s, CHN); δ_C (75MHz, $CDCl_3$) 29.5, 32.1, 56.3, 61.3, 63.1, 109.1, 110.7, 123.5, 129.3, 149.7, 151.8, 161.2; *m/z* (ES^+) 238.1437 ($[M+H]^+$ - $C_{13}H_{20}NO_3$ requires 238.1438) (CI^+) 238.1 [M+H] (100%).

4-(Benzylideneamino)butan-1-ol 165[161]



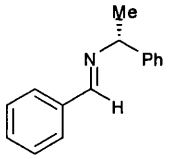
Yellow oil (100%), δ_H (300MHz, $CDCl_3$) 1.70 (4H, m, 2 x C*H*$_2$), 3.59 (4H, m, 2 x C*H*$_2$), 3.93 (1H, br s, CH_2O*H*), 7.28-7.40 (3H, m, Ar*H*), 7.56-7.70 (2H, m, Ar*H*), 8.23 (1H, s, C*H*N); δ_C (75MHz, $CDCl_3$) 27.9, 30.6, 60.2, 61.7, 127.2, 127.7, 129.8, 134.7, 160.3; *m/z* (ES^+) 178.1227 ($[M+H]^+$ - $C_{11}H_{16}NO$ requires 178.1226) (CI^+) 178.1 [M+H] (100%).

***N*-Benzylidenebutan-1-amine 166[162]**



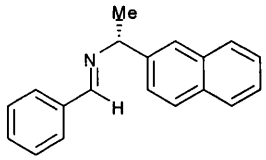
Yellow oil (69%), δ_H (300MHz, $CDCl_3$) 0.86 (3H, t, *J* = 7.2, CH_2CH_3), 1.23-1.37 (2H, m, CH_2CH_3), 1.55–1.66 (2H, m, $CH_2CH_2CH_3$), 3.52 (2H, t, *J* = 7.2, NCH_2CH_2) 7.27-7.34 (3H, m, Ar*H*), 7.60-7.67 (2H, m, Ar*H*), 8.17 (1H, s, C*H*N); δ_C (75MHz, $CDCl_3$) 14.3, 20.9, 33.4, 61.9, 128.4, 129.0, 130.9, 136.7, 161.2; *m/z* (ES^+) 162.1277 ($[M+H]^+$ - $C_{11}H_{16}N$ requires 162.1277).

(*R*)-*N*-Benzylidene-1-phenylethanamine 101[163]



Clear oil (95%), $[\alpha]_D^{25}$ = -72.8 (c 2.3, $CHCl_3$) [Lit., -73 (c 2.3, $CHCl_3$)]; δ_H (300MHz, $CDCl_3$) 1.69 (3H, d, *J* = 6.6, C*H*$_3$), 4.64 (1H, q, *J* = 6.6, C*H*CH_3), 7.24-7.36 (1H, m, Ar*H*), 7.38-7.57 (7H, m, Ar*H*), 7.84-7.91 (2H, m, Ar*H*), 8.04-8.10 (2H, m, Ar*H*) 8.58 (1H, s, C*H*N); δ_C (75MHz, $CDCl_3$) 25.3, 70.1, 127.0, 127.2, 128.7, 128.8, 129.1, 131.0, 136.8, 145.6, 159.9; *m/z* (ES^+) 210.1277 ($[M+H]^+$ - $C_{15}H_{16}N$ requires 210.1277) (CI^+) 210.1 [M+H] (100%).

(*R*)-*N*-Benzylidene-1-(naphthalen-2-yl)ethanamine 148



White solid (99%), mp 85-87 °C; $[\alpha]_D^{25}$ = -42.0 (c 0.5, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1644 (C=N); δ_H (300MHz, $CDCl_3$) 1.70 (3H, d, *J* = 6.8, C*H*$_3$), 4.73 (1H, q, *J* = 6.8, C*H*CH_3), 7.38-7.49 (5H, m, Ar*H*), 7.58-7.63 (1H, m, Ar*H*), 7.79-7.89 (6H, m, Ar*H*), 8.44 (1H, s, C*H*N); δ_C (75MHz, $CDCl_3$) 25.2, 70.2, 125.3, 125.9, 126.3, 128.3, 128.5, 128.7, 128.9, 131.1, 133.0, 133.9, 136.8, 143.0, 160.2; 159.9; *m/z* (ES^+) 260.1435 ($[M+H]^+$ - $C_{19}H_{18}N$ requires 260.1434) (CI^+) 260.2 [M+H] (100%).

7.3 Synthesis of 2,3-dihydropyridin-4-ones

The following pyridones were synthesised according to the general procedures described in sections **7.3.1** – **7.3.7**.

7.3.1 Synthesis of dihydropyridones using original literature procedure

To a suspension of powdered 4Å molecular sieves (1.0 g) in CH_2Cl_2 were added (*R*)-BINOL (100 mg, 0.35 mmol) and $B(OPh)_3$ (101 mg, 0.35 mmol) at room temperature under nitrogen. After stirring for 1 h, the mixture was cooled to 0 °C and a solution of imine (0.35 mmol) in CH_2Cl_2 (1 ml) was added. After stirring for 10 min at the same temperature, the mixture was cooled to -78 °C, and a solution of Danishefsky's diene (0.084 ml, 0.42 mmol) in CH_2Cl_2 (1 ml) was added dropwise. After stirring for 5 h, the solution was washed with saturated $NaHCO_3$, and then dried over $MgSO_4$. Evaporation of solvent and purification by column chromatography on silica gel gave the corresponding dihydropyridone.

7.3.2 Standard procedure for the boron-BINOL catalysed aza Diels-Alder reaction at – 78 °C

To a suspension of powdered 4Å molecular sieves (1.0 g) in CH_2Cl_2 were added (*R*)-BINOL (144 mg, 0.50 mmol) and $B(OMe)_3$ (0.028 ml, 0.25 mmol) at room temperature

under nitrogen. After stirring for 1 h, the mixture was cooled to 0 °C and a solution of imine (0.25 mmol) in CH_2Cl_2 (1 ml) was added. After stirring for 10 min at the same temperature, the mixture was cooled to -78 °C, and a solution of Danishefsky's diene (0.049 ml, 0.25 mmol) in CH_2Cl_2 (1 ml) was added dropwise. After stirring for 5 h, the solution was washed with saturated $NaHCO_3$, and then dried over $MgSO_4$. Evaporation of solvent and purification by column chromatography on silica gel gave the corresponding dihydropyridone.

7.3.3 Standard procedure for the boron-BINOL catalysed aza Diels-Alder reaction at room temperature

To a suspension of powdered 4Å molecular sieves (1.0 g) in CH_2Cl_2 were added (*R*)-BINOL (144 mg, 0.50 mmol) and $B(OMe)_3$ (0.028 ml, 0.25 mmol) at room temperature under nitrogen. After stirring for 1 h, a solution of imine (0.25 mmol) in CH_2Cl_2 (1 ml) was added. After stirring for 10 min, the mixture was cooled to -78 °C, and a solution of Danishefsky's diene (0.049 ml, 0.25 mmol) in CH_2Cl_2 (1 ml) was added dropwise. After stirring for 5 h, the solution was washed with saturated $NaHCO_3$, and then dried over $MgSO_4$. Evaporation of solvent and purification by column chromatography on silica gel gave the corresponding dihydropyridone.

7.3.4 Preparation of dihydropyridones employing reaction additives

To a suspension of powdered 4Å molecular sieves (1.0 g) in CH_2Cl_2 were added (*R*)-BINOL (144 mg, 0.50 mmol), $B(OMe)_3$ (0.028 ml, 0.25 mmol) and the required additive (0.25 mmol) at room temperature under nitrogen. After stirring for 1 h, a solution of imine (0.25 mmol) in CH_2Cl_2 (1 ml) was added. After stirring for 10 min, the mixture was cooled to -78 °C, and a solution of Danishefsky's diene (0.049 ml, 0.25 mmol) in CH_2Cl_2 (1 ml) was added dropwise. After stirring for 5 h, the solution was washed with saturated $NaHCO_3$, and then dried over $MgSO_4$. Evaporation of solvent and purification by column chromatography on silica gel gave the corresponding dihydropyridone.

7.3.5 Preparation of dihydropyridones employing BINOL derived chiral ligands

To a suspension of powdered 4Å molecular sieves (1.0 g) in CH_2Cl_2 were added (*R*)-BINOL-type ligand (0.50 mmol), $B(OMe)_3$ (0.028 ml, 0.25 mmol) and the required additive (0.25 mmol) at room temperature under nitrogen. After stirring for 1 h, a

solution of imine (0.25 mmol) in CH_2Cl_2 (1 ml) was added. After stirring for 10 min, the mixture was cooled to -78 °C, and a solution of Danishefsky's diene (0.049 ml, 0.25 mmol) in CH_2Cl_2 (1 ml) was added dropwise. After stirring for 5 h, the solution was washed with saturated $NaHCO_3$, and then dried over $MgSO_4$. Evaporation of solvent and purification by column chromatography on silica gel gave the corresponding dihydropyridone.

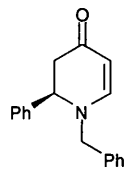
7.3.6 Preparation of dihydropyridones using the inverse addition technique

To a suspension of powdered 4Å molecular sieves (1.0 g) in CH_2Cl_2 were added (*R*)-BINOL (144 mg, 0.50 mmol), imine (0.25 mmol) and Danishefsky's diene (0.049 ml, 0.25 mmol) under nitrogen. After stirring for 5 min, $B(OMe)_3$ (0.28 ml, 0.25 mmol) was added dropwise using a syringe pump over a 25 min to 8 h period. The reaction mixture was stirred for a further 5 h, and then the solution was washed with saturated $NaHCO_3$, and then dried over $MgSO_4$. Evaporation of solvent and purification by column chromatography on silica gel gave the corresponding dihydropyridone.

7.3.7 Preparation of dihydropyridones using BINOL-propeller boronate 117

Imine (0.50 mmol) was added to a stirred solution of propeller boronate **117** (0.50 mmol) in either CH_2Cl_2 or $CHCl_3$. After stirring for 10 min, the mixture was cooled to -78 °C, and a solution of Danishefsky's diene (0.098 ml, 0.50 mmol) in CH_2Cl_2 (1 ml) was added dropwise. After stirring for 5 h, the solution was washed with saturated $NaHCO_3$, and then dried over $MgSO_4$. Evaporation of solvent and purification by column chromatography on silica gel gave the corresponding dihydropyridone. The same procedure was also carried out entirely at room temperature.

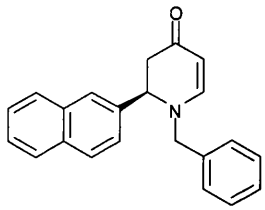
1-Benzyl-2-phenyl-2,3-dihydropyridin-4(1H)-one 26[24]



Purification by column chromatography (SiO_2, 60:40 EtOAc:PE) afforded the title compound as a yellow oil (70%), $[\alpha]_D^{25}$ = -4.5 (c 1.0, $CHCl_3$) for 74% ee (lit., $[\alpha]_D^{25}$ = -4.7 (c 1.0, $CHCl_3$) for 83% ee; ν_{max}(neat)/cm^{-1} 1644 (C=O); δ_H (300MHz, $CDCl_3$) 2.69 (1H, dd, *J* = 16.6, 7.9, PhCHCH_ACH_BCO), 2.84 (1H, dd, *J* = 16.6, 7.2,

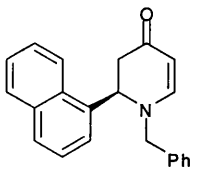
PhCHCH$_A$CH_BCO), 4.12 (1H, d, J = 15.0, CH_ACH$_B$Ph), 4.34 (1H, d, J = 15.0, CH$_A$CH_BPh), 4.49 (1H, app t, J = 7.6, PhCHCH$_A$CH$_B$CO), 5.08 (1H, d, J = 7.6, COCH=CH), 7.09-7.15 (2H, m, COCH=CH + ArH), 7.24-7.40 (9H, m, ArH); δ_C (75MHz, $CDCl_3$) 44.1, 57.1, 61.2, 99.2, 127.5, 128.1, 128.6, 129.3, 129.4, 136.3, 136.9, 154.6, 190.8; HPLC (Daicel Chiralcel AD with 97:3 Hex:IPA) t_r = 52.8, 59.3 min; *m/z* (ES^+) 264.1382 ($[M+H]^+$ - $C_{18}H_{18}NO$ requires 264.1383) (CI^+) 264.2 [M+H] (100%).

1-Benzyl-2-(naphthalen-2-yl)-2,3-dihydropyridin-4(1H)-one 167[24]



Purification by column chromatography (SiO_2, 60:40 EtOAc:PE) afforded the title compound as a yellow oil (65%), $[\alpha]_D^{25}$ = -37.0 (c 1.2, $CHCl_3$) for 82% ee (lit., $[\alpha]_D^{25}$ = -38.2 (c 1.2, $CHCl_3$) for 84% ee; δ_H (300MHz, $CDCl_3$) 2.80 (1H, dd, J = 16.6, 6.8, ArCHCH_ACH$_B$CO), 2.89 (1H, dd, J = 16.6, 6.0, ArCHCH$_A$CH_BCO), 4.14 (1H, d, J = 15.0, CH_ACH$_B$Ph), 4.38 (1H, d, J = 15.0, CH$_A$CH_BPh), 4.67 (1H, app t, J = 6.5, ArCHCH$_A$CH$_B$CO), 5.14 (1H, d, J = 7.2, COCH=CH), 7.07-7.16 (2H, m, COCH=CH + ArH), 7.30-7.39 (4H, m, ArH), 7.41-7.46 (1H, m, ArH), 7.48-7.55 (2H, m, ArH), 7.60-7.63 (1H, m, ArH), 7.74-7.90 (3H, m, ArH); δ_C (75MHz, $CDCl_3$) 44.6, 57.7, 61.4, 99.3, 124.9, 126.6, 126.8, 127.0, 128.1, 128.2, 128.3, 129.3, 129.6, 133.5, 136.5, 154.7, 190.8; HPLC (Daicel Chiralcel AD with 90:10 Hex:IPA) t_r = 25.1, 31.3 min; *m/z* (ES^+) 314.1538 ($[M+H]^+$ - $C_{22}H_{20}NO$ requires 314.1539) (CI^+) 314.2 [M+H] (100%).

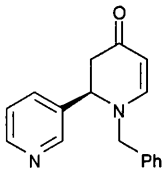
1-Benzyl-2-(naphthalen-1-yl)-2,3-dihydropyridin-4(1H)-one 168



Purification by column chromatography (SiO_2, 50:50 EtOAc:PE) afforded the title compound as a yellow oil (85%), ν_{max}(neat)/cm^{-1} 1638 (C=O); δ_H (300MHz, $CDCl_3$) 2.87 (2H, d, J = 7.9, ArCHCH_2CO), 4.04 (1H, d, J = 15.1, CH_ACH$_B$Ph), 4.32 (1H, d, J = 15.1, CH$_A$CH_BPh), 5.07 (1H, d, J = 7.5, COCH=CH), 5.21 (1H, app t, J = 7.9,

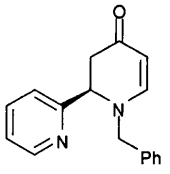
ArC*H*CH$_A$CH$_B$CO), 6.97-7.03 (2H, m, COCH=C*H* + Ar*H*), 7.21-7.50 (8H, m, Ar*H*), 7.72-7.90 (3H, m, Ar*H*); δ_C (75MHz, $CDCl_3$) 41.4, 56.5, 97.5, 121.5, 124.8, 125.5, 126.8, 127.2, 128.4, 129.4, 131.8, 133.4, 134.8, 153.4, 189.3; HPLC (Daicel Chiralcel AD with 90:10 Hex:IPA) t_r = 20.6, 21.3 min; *m/z* (ES^+) 314.1534 ($[M+H]^+$ - $C_{22}H_{20}NO$ requires 314.1539) (CI^+) 314.2 [M+H] (100%).

1-Benzyl-2-(pyridin-3-yl)-2,3-dihydropyridin-4(1H)-one 169[24]



Purification by column chromatography (SiO_2, EtOAc) afforded the title compound as a yellow oil (60%), $[\alpha]_D^{25}$ = -36.6 (c 1.0, $CHCl_3$) for 83% ee (lit., $[\alpha]_D^{25}$ = -39.4 (c 1.0, $CHCl_3$) for 90% ee; δ_H (300MHz, $CDCl_3$) 2.55 (1H, dd, *J* = 16.2, 7.2, PhCHC*H*$_A$CH$_B$CO), 2.84 (1H, dd, *J* = 16.2, 7.2, PhCHCH$_A$C*H*$_B$CO), 4.05 (1H, d, *J* = 15.1, C*H*$_A$CH$_B$Ph), 4.34 (1H, d, *J* = 15.1, CH$_A$C*H*$_B$Ph), 4.47 (1H, app t, *J* = 7.2, PhC*H*CH$_A$CH$_B$CO), 5.08 (1H, d, *J* = 7.6, COC*H*=CH), 7.03-7.13 (2H, m, COCH=C*H* + Ar*H*), 7.19-7.37 (5H, m, Ar*H*), 7.55-7.63 (1H, m, Ar*H*), 8.35-8.42 (1H, m, Ar*H*), 8.50-8.55 (1H, m, Ar*H*); δ_C (75MHz, $CDCl_3$) 43.5, 58.1, 58.4, 99.5, 124.3, 128.1, 128.9, 129.5, 134.5, 135.0, 135.8, 149.1, 150.3, 154.5,189.9; HPLC (Daicel Chiralcel OD with 65:35 Hex:IPA) t_r = 17.3, 33.0 min; *m/z* (ES^+) 265.1334 ($[M+H]^+$ - $C_{17}H_{17}N_2O$ requires 265.1335) (CI^+) 265.1 [M+H] (100%).

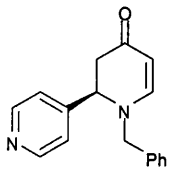
1-Benzyl-2-(pyridin-2-yl)-2,3-dihydropyridin-4(1H)-one 170



Purification by column chromatography (SiO_2, 90:10 EtOAc:MeOH) afforded the title compound as a yellow oil (40%), ν_{max}(neat)/cm^{-1} 1644 (C=O); δ_H (300MHz, $CDCl_3$) 2.76 (1H, dd, *J* = 16.5, 7.5, PhCHC*H*$_A$CH$_B$CO), 2.86 (1H, dd, *J* = 16.5, 7.5,

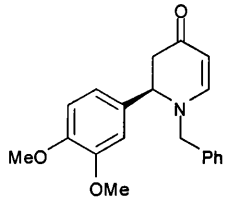
PhCHCH$_A$C*H*$_B$CO), 4.24 (1H, d, *J* = 15.1, C*H*$_A$CH$_B$Ph), 4.39 (1H, d, *J* = 15.1, CH$_A$C*H*$_B$Ph), 4.65 (1H, app t, *J* = 7.5, PhC*H*CH$_A$CH$_B$CO), 4.99 (1H, d, *J* = 7.5, COC*H*=CH), 7.08-7.35 (8H, m, COCH=C*H* + Ar*H*), 7.56-7.64 (1H, m, Ar*H*), 8.53-8.57 (1H, m, Ar*H*); δ_C (75MHz, $CDCl_3$) 41.9, 58.6, 61.8, 99.0, 121.8, 123.4, 128.2, 128.7, 129.4, 136.3, 137.4, 150.4, 154.1, 158.0, 190.4; HPLC (Daicel Chiralcel OD with 85:15 Hex:IPA) t_r = 17.3, 33.0 min; *m/z* (ES^+) 265.1334 ($[M+H]^+$ - $C_{17}H_{17}N_2O$ requires 265.1335) (CI^+) 265.1 [M+H] (100%).

1-Benzyl-2-(pyridin-4-yl)-2,3-dihydropyridin-4(1H)-one 171



Purification by column chromatography (SiO_2, 90:10 EtOAc:MeOH) afforded the title compound as a yellow oil (36%), ν_{max}(neat)/cm^{-1} 1644 (C=O); δ_H (300MHz, $CDCl_3$) 2.57 (1H, dd, *J* = 16.6, 6.0, PhCHC*H*$_A$CH$_B$CO), 2.92 (1H, dd, *J* = 16.6, 7.5, PhCHCH$_A$C*H*$_B$CO), 4.13 (1H, d, *J* = 15.1, C*H*$_A$CH$_B$Ph), 4.43 (1H, d, *J* = 15.1, CH$_A$C*H*$_B$Ph), 4.49 (1H, app t, *J* = 6.0, PhC*H*CH$_A$CH$_B$CO), 5.10 (1H, d, *J* = 7.5, COC*H*=CH), 7.13-7.19 (4H, m, COCH=C*H* + Ar*H*), 7.31-7.41 (4H, m, Ar*H*), 8.57-8.62 (2H, m, Ar*H*); δ_C (75MHz, $CDCl_3$) 43.0, 58.3, 59.7, 99.7, 122.2, 128.1, 129.0, 129.5, 135.7, 147.8, 150.9, 154.2, 189.4; HPLC (Daicel Chiralcel OD with 80:20 Hex:IPA) t_r = 12.1, 13.9 min; *m/z* (ES^+) 265.1334 ($[M+H]^+$ - $C_{17}H_{17}N_2O$ requires 265.1335) (CI^+) 265.1 [M+H] (100%).

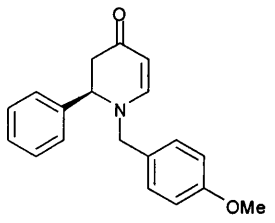
1-Benzyl-2-(3,4-dimethoxyphenyl)-2,3-dihydropyridin-4(1H)-one 172



Purification by column chromatography (SiO_2, 70:30 EtOAc:PE) afforded the title compound as a yellow oil (55%), ν_{max}(neat)/cm^{-1} 1639 (C=O); δ_H (300MHz, $CDCl_3$)

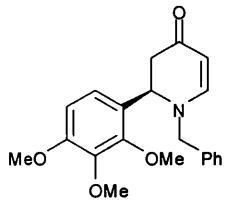
2.66 (1H, dd, J = 16.6, 9.0, PhCHCH_ACH$_B$CO), 2.74 (1H, dd, J = 16.6, 7.2, PhCHCH$_A$CH_BCO), 3.76 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 4.08 (1H, d, J = 15.1, CH_ACH$_B$Ph), 4.28 (1H, d, J = 15.1, CH$_A$CH_BPh), 4.40 (1H, dd, J = 9.0, 7.2, PhCHCH$_A$CH$_B$CO), 5.05 (1H, d, J = 7.9, COCH=CH), 6.66-6.69 (1H, m, ArH), 6.71-6.81 (2H, m, ArH), 7.04-7.10 (2H, m, COCH=CH + ArH), 7.23 (1H, m, ArH), 7.27-7.34 (3H, m, ArH); δ_C (75MHz, $CDCl_3$) 44.3, 56.2, 57.4, 61.1, 99.0, 110.5, 111.6, 120.1, 128.1, 128.5, 128.9, 131.02, 136.4, 149.3, 149.6, 154.8, 191.2; HPLC (Daicel Chiralcel AD with 80:20 Hex:IPA) t_r = 12.2, 15.4 min; *m/z* (ES^+) 324.1598 ($[M+H]^+$ - $C_{20}H_{22}NO_3$ requires 324.1594) (CI^+) 324.2 [M+H] (100%).

1-(4-Methoxybenzyl)-2-phenyl-2,3-dihydropyridin-4(1H)-one 173



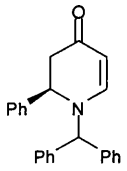
Purification by column chromatography (SiO_2, 60:40 EtOAc:PE) afforded the title compound as a yellow oil (49%), ν_{max}(neat)/cm^{-1} 1646 (C=O); δ_H (300MHz, $CDCl_3$) 2.59 (1H, dd, J = 16.2, 8.2, PhCHCH_ACH$_B$CO), 2.75 (1H, dd, J = 16.6, 7.2, PhCHCH$_A$CH_BCO), 3.74 (3H, s, OCH_3), 3.99 (1H, d, J = 15.1, CH_ACH$_B$Ph), 4.20 (1H, d, J = 15.1, CH$_A$CH_BPh), 4.40 (1H, app t, J = 7.5, PhCHCH$_A$CH$_B$CO), 4.99 (1H, d, J = 7.9, COCH=CH), 6.77-6.84 (2H, m, ArH), 6.93-6.99 (2H, m, ArH), 7.14-7.33 (6H, m, COCH=CH + ArH); δ_C (75MHz, $CDCl_3$) 44.1, 55.7, 57.1, 61.0, 98.7, 114.7, 127.5, 128.7, 129.4, 129.6, 139.1, 154.4, 190.8; *m/z* (ES^+) 294.1487 ($[M+H]^+$ - $C_{19}H_{20}NO_3$ requires 294.1489) (CI^+) 294.2 [M+H] (100%).

1-Benzyl-2-(2,3,4-trimethoxyphenyl)-2,3-dihydropyridin-4(1H)-one 174



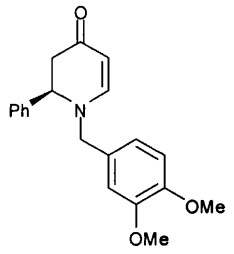
Purification by column chromatography (SiO_2, EtOAc) afforded the title compound as a yellow oil (50%), ν_{max}(neat)/cm^{-1} 1634 (C=O); δ_H (300MHz, $CDCl_3$) 2.54 (1H, dd, J = 16.6, 6.8, PhCHCH_ACH$_B$CO), 2.79 (1H, dd, J = 16.6, 7.5, PhCHCH$_A$CH_BCO), 3.66 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 4.11 (1H, d, J = 15.1, CH_ACH$_B$Ph), 4.27 (1H, d, J = 15.1, CH$_A$CH_BPh), 4.81 (1H, app t, J = 7.2, PhCHCH$_A$CH$_B$CO), 5.00 (1H, d, J = 7.5, COCH=CH), 6.55-6.59 (1H, m, ArH), 6.93-6.98 (1H, m, ArH), 7.07-7.12 (2H, m, COCH=CH + ArH), 7.20-7.35 (4H, m, ArH); δ_C (75MHz, $CDCl_3$) 43.0, 54.6, 56.4, 57.3, 60.8, 61.3, 98.4, 107.7, 122.2, 124.1, 128.6, 129.3, 136.6, 142.6, 151.8, 154.0, 154.8, 191.0; HPLC (Daicel Chiralcel AD with 90:10 Hex:IPA) t_r = 23.5, 26.3 min; *m/z* (ES$^+$) 354.1705 ([M+H]$^+$ - $C_{21}H_{24}NO_4$ requires 354.1700) (CI$^+$) 354.2 [M+H] (100%).

1-Benzhydryl-2-phenyl-2,3-dihydropyridin-4(1H)-one 175



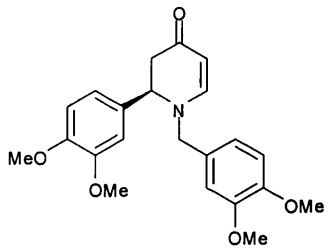
Purification by column chromatography (SiO_2, 40:60 EtOAc:PE) afforded the title compound as a yellow oil (11%), ν_{max}(neat)/cm^{-1} 1646 (C=O); δ_H (300MHz, $CDCl_3$) 2.70 (1H, dd, J = 16.6, 9.0, PhCHCH_ACH$_B$CO), 2.81 (1H, dd, J = 16.6, 6.8, PhCHCH$_A$CH_BCO), 4.49 (1H, dd, J = 9.0, 6.8, PhCHCH$_A$CH$_B$CO), 4.97 (1H, d, J = 7.9, COCH=CH), 5.37 (1H, s, CHPh$_2$), 6.93-6.98 (2H, m, ArH), 7.02 (1H, d, J = 7.9, COCH=CH), 7.05-7.12 (2H, m, ArH), 7.21-7.39 (11H, m, ArH); δ_C (75MHz, $CDCl_3$) 62.7, 68.3, 99.3, 127.7, 128.0, 128.6, 129.2, 129.4, 129.6, 130.0, 138.6, 139.4, 151.9, 190.8; *m/z* (ES$^+$) 340.1694 ([M+H]$^+$ - $C_{24}H_{22}NO$ requires 340.1696) (CI$^+$) 340.1 [M+H] (100%).

1-(3,4-Dimethoxybenzyl)-2-phenyl-2,3-dihydropyridin-4(1H)-one 176[24]



Purification by column chromatography (SiO_2, 70:30 EtOAc:PE) afforded the title compound as a yellow oil (25%), $[\alpha]_D^{25}$ = -6.1 (c 3.0, $CHCl_3$) (lit., $[\alpha]_D^{25}$ = -28.9 (c 3.2, $CHCl_3$) for 85% ee; δ_H (300MHz, $CDCl_3$) 2.61 (1H, dd, *J* = 16.2, 8.3, PhCHCH_ACH$_B$CO), 2.76 (1H, dd, *J* = 16.2, 6.8, PhCHCH$_A$CH_BCO), 3.75 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 4.00 (1H, d, *J* = 15.1, CH_ACH$_B$Ph), 4.22 (1H, d, *J* = 15.1, CH$_A$CH_BPh), 4.42 (1H, app t, *J* = 8.3, PhC*H*CH$_A$CH$_B$CO), 5.02 (1H, d, *J* = 7.5, COC*H*=CH), 6.47 (1H, m Ar*H*), 6.58-6.64 (1H, m, Ar*H*), 6.76 (1H, m, Ar*H*), 7.15-7.35 (6H, m, COCH=C*H* + Ar*H*); δ_C (75MHz, $CDCl_3$) 42.1, 54.2, 55.5, 58.9, 97.0, 109.2, 109.6, 125.5, 126.4, 126.6, 127.3, 137.0, 147.3, 147.6, 152.4, 188.7; *m/z* (ES^+) 324.1596 ($[M+H]^+$ - $C_{20}H_{22}NO_3$ requires 324.1594) (CI^+) 324.2 [M+H] (100%).

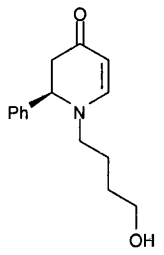
1-(3,4-Dimethoxybenzyl)-2-(3,4-dimethoxyphenyl)-2,3-dihydropyridin-4(1H)-one 177



Purification by column chromatography (SiO_2, EtOAc) afforded the title compound as a yellow oil (65%), ν_{max}(neat)/cm^{-1} 1635 (C=O); δ_H (300MHz, $CDCl_3$) 2.60 (1H, dd, *J* = 16.6, 9.0, PhCHCH_ACH$_B$CO), 2.69 (1H, dd, *J* = 16.6, 6.8, PhCHCH$_A$CH_BCO), 3.73 (6H, s, 2 x OCH_3), 3.79 (6H, s, 2 x OCH_3), 3.99 (1H, d, *J* = 15.1, CH_ACH$_B$Ph), 4.20 (1H, d, *J* = 15.1, CH$_A$CH_BPh), 4.35 (1H, dd, *J* = 9.0, 6.8, PhC*H*CH$_A$CH$_B$CO), 4.99 (1H, d, *J* = 7.5, COC*H*=CH), 6.46-6.48 (1H, m, Ar*H*), 6.57-6.62 (1H, m, Ar*H*), 6.66-6.78 (4H, m, Ar*H*), 7.23 (1H, d, *J* = 7.5, COCH=C*H*); δ_C (75MHz, $CDCl_3$) 44.3, 56.3, 57.3, 60.9, 98.8, 110.5, 111.2, 111.6, 119.5, 120.1, 120.6, 128.6, 131.5, 149.3, 149.7, 154.7,

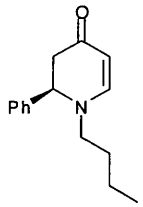
191.2; HPLC (Daicel Chiralcel OD with 65:35 Hex:IPA) t_r = 34.2, 42.2 min; *m/z* (ES^+) 383.1804 ($[M+H]^+$ - $C_{22}H_{26}NO_5$ requires 383.1805) (CI^+) 384.2 [M+H] (100%).

1-(4-Hydroxybutyl)-2-phenyl-2,3-dihydropyridin-4(1H)-one 178



Purification by column chromatography (SiO_2, EtOAc) afforded the title compound as a yellow oil (73%), ν_{max}(neat)/cm^{-1} 3534 (OH), 1620 (C=O); δ_H (300MHz, $CDCl_3$) 1.57 (4H, m, 2 x CH_2), 2.63 (1H, dd, *J* = 16.6, 8.3, PhCHCH_ACH$_B$CO), 2.79 (1H, dd, *J* = 16.6, 6.8, PhCHCH$_A$CH_BCO), 3.06 (2H, m, NCH_2CH$_2$), 3.73 (2H, m, CH$_2$CH_2OH), 4.54 (1H, dd, *J* = 8.3, 6.8, PhC*H*CH$_A$CH$_B$CO), 4.99 (1H, d, *J* = 7.5, COC*H*=CH), 7.09 (1H, d, *J* = 7.5, COCH=C*H*), 7.20-7.45 (5H, m, Ar*H*); δ_C (75MHz, $CDCl_3$) 26.1, 35.9, 41.9, 50.3, 54.1, 68.9, 92.9, 128.0, 129.2, 129.9, 133.6, 153.6, 188.2; *m/z* (ES^+) 246.1491 ($[M+H]^+$ - $C_{15}H_{20}NO_2$ requires 246.1489).

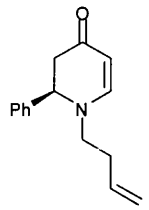
1-Butyl-2-phenyl-2,3-dihydropyridin-4(1H)-one 179



Purification by column chromatography (SiO_2, 70:30 EtOAc:PE) afforded the title compound as a yellow oil (71%), ν_{max}(neat)/cm^{-1} 1660 (C=O); δ_H (300MHz, $CDCl_3$) 0.88 (5H, m, CH2CH_3 + CH_2CH$_3$), 1.50 (2H, app quin, *J* = 7.2, CH_2CH$_2$CH$_3$), 2.67 (1H, dd, *J* = 16.2, 7.9, PhCHCH_ACH$_B$CO), 2.88 (1H, dd, *J* = 16.2, 7.2, PhCHCH$_A$CH_BCO), 3.08 (2H, t, *J* = 7.2, NCH_2CH$_2$), 4.61 (1H, app t, *J* = 7.2, PhC*H*CH$_A$CH$_B$CO), 5.01 (1H, d, *J* = 7.5, COC*H*=CH), 7.16 (1H, d, *J* = 7.5, COCH=C*H*), 7.23-7.39 (5H, m, Ar*H*); δ_C (75MHz, $CDCl_3$) 14.6, 20.1, 31.2, 44.1, 60.8, 53.8, 98.4, 127.3, 128.6, 129.4, 139.1,

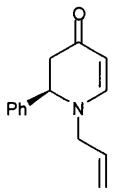
154.6, 190.5; HPLC (Daicel Chiralcel AD with 90:10 Hex:IPA) t_r = 13.2, 14.4 min; *m/z* (ES^+) 230.1539 ($[M+H]^+$ - $C_{15}H_{20}NO$ requires 230.1539) (CI^+) 230.2 [M+H] (100%).

1-(But-3-enyl)-2-phenyl-2,3-dihydropyridin-4(1H)-one 180



Purification by column chromatography (SiO_2, 60:40 EtOAc:PE) afforded the title compound as a yellow oil (17%), ν_{max}(neat)/cm^{-1} 1661 (C=O); δ_H (300MHz, $CDCl_3$) 2.20 (2H, m, CH_2CH_2CH=), 2.60 (1H, dd, *J* = 16.6, 7.9, PhCHC$H_A$$CH_B$CO), 2.79 (1H, dd, *J* = 16.6, 7.2, PhCHCH_ACH_BCO), 3.10 (2H, t, *J* = 7.2, NC$H_2$$CH_2$), 4.56 (1H, app t, *J* = 7.5, PhC*H*$CH_A$$CH_B$CO), 4.95 (1H, d, *J* = 7.5, COC*H*=CH), 4.98-5.07 (2H, m, CH=CH_2), 5.54-5.70 (1H, m, C*H*=CH_2), 7.07 (1H, d, *J* = 7.5, COCH=C*H*), 7.21-7.35 (5H, m, Ar*H*); δ_C (75MHz, $CDCl_3$) 33.7, 44.1, 61.5, 98.7, 118.6, 127.3, 128.7, 129.4, 134.4, 139.0, 154.5, 194.6; HPLC (Daicel Chiralcel OD with 90:10 Hex:IPA) t_r = 26.6, 31.9 min; *m/z* (ES^+) 228.1383 ($[M+H]^+$ - $C_{15}H_{18}NO$ requires 228.1383).

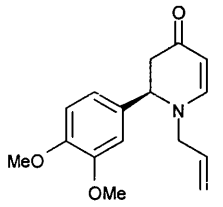
1-Allyl-2-phenyl-2,3-dihydropyridin-4(1H)-one 181[24]



Purification by column chromatography (SiO_2, 70:30 EtOAc:PE) afforded the title compound as a yellow oil (65%), $[\alpha]_D^{25}$ = -189.1 (c 1.0, $CHCl_3$) for 77% ee (lit., $[\alpha]_D^{25}$ = -187.7 (c 1.0, $CHCl_3$) for 70% ee; δ_H (300MHz, $CDCl_3$) 2.72 (1H, dd, *J* = 16.6, 8.7, PhCHC$H_A$$CH_B$CO), 2.88 (1H, dd, *J* = 16.6, 6.8, PhCHCH_ACH_BCO), 3.58 (1H, dd, *J* = 15.4, 7.2, NC$H_A$$CH_B$CH), 3.73 (1H dd, *J* = 15.4, 4.9, NCH_ACH_BCH), 4.56 (1H, dd, *J* = 8.7, 6.8, PhC*H*$CH_A$$CH_B$CO), 5.09 (1H, d, *J* = 7.5, COC*H*=CH), 5.12-5.29 (2H, m, CH=CH_2), 5.70-5.85 (1H, m, C*H*=CH_2), 7.19 (1H, d, *J* = 7.5, COCH=C*H*), 7.29-7.45 (5H, m, Ar*H*); δ_C (75MHz, $CDCl_3$) 44.21, 55.9, 61.6, 99.4, 119.6, 127.4, 128.7, 129.4,

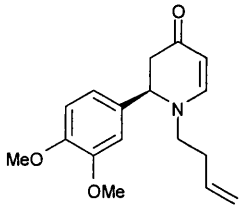
133.1, 139.2, 154.3, 190.9; HPLC (Daicel Chiralcel OD with 80:20 Hex:IPA) t_r = 10.9, 12.2 min; *m/z* (ES^+) 214.1225 ($[M+H]^+$ - $C_{14}H_{16}NO$ requires 214.1226) (CI^+) 214.1 [M+H] (100%).

1-Allyl-2-(3,4-dimethoxyphenyl)-2,3-dihydropyridin-4(1H)-one 182



Purification by column chromatography (SiO_2, 70:30 EtOAc:PE) afforded the title compound as a yellow solid (55%), mp 94-96 °C; $\nu_{max}(CHCl_3)/cm^{-1}$ 1634 (C=O); δ_H (300MHz, $CDCl_3$) 2.65 (1H, dd, *J* = 16.6, 9.0, PhCHCH_ACH$_B$CO), 2.76 (1H, dd, *J* = 16.6, 6.8, PhCHCH$_A$CH_BCO), 3.51 (1H, dd, *J* = 15.8, 7.2, NCH_ACH$_B$CH), 3.65 (1H dd, *J* = 15.8, 4.9, NCH$_A$CH_BCH), 3.80 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 4.50 (1H, dd, *J* = 9.0, 6.8, PhC*H*CH$_A$CH$_B$CO), 5.00 (1H, d, *J* = 7.5, COC*H*=CH), 5.06-5.22 (2H, m, CH=CH_2), 5.63-5.77 (1H, m, C*H*=CH$_2$), 6.78 (3H, s, Ar*H*), 7.11 (1H, d, *J* = 7.5, COCH=C*H*); δ_C (75MHz, $CDCl_3$) 44.37, 55.7, 56.3, 61.5, 99.2, 110.3, 111.7, 119.4, 120.0, 131.64, 133.3, 149.4, 149.8, 154.3, 191.1; HPLC (Daicel Chiralcel OD with 85:15 Hex:IPA) t_r = 80.6, 86.6 min; *m/z* (ES^+) 274.1435 ($[M+H]^+$ - $C_{16}H_{20}NO_3$ requires 274.1438) (CI^+) 273.1 [M+H] (100%).

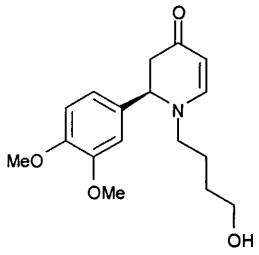
1-(But-3-enyl)-2-(3,4-dimethoxyphenyl)-2,3-dihydropyridin-4(1H)-one 183



Purification by column chromatography (SiO_2, 70:30 EtOAc:PE) afforded the title compound as a yellow oil (10%), ν_{max}(neat)/cm^{-1} 1662 (C=O); δ_H (300MHz, $CDCl_3$) 2.21-2.30 (2H, m, CH_2CH_2CH=), 2.67 (1H, dd, *J* = 16.2, 8.7, PhCHCH_ACH$_B$CO), 2.81 (1H, dd, *J* = 16.2, 6.8, PhCHCH$_A$CH_BCO), 3.14 (2H, td, *J* = 7.2, 1.8, NCH_2CH$_2$), 3.87 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 4.56 (1H, dd, *J* = 8.7, 6.8, PhC*H*CH$_A$CH$_B$CO), 5.01

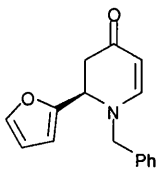
(1H, d, *J* = 7.5, COC*H*=CH), 5.04-5.11 (2H, m, CH=CH_2), 5.58-5.76 (1H, m, C*H*=CH_2), 6.80-6.87 (3H, m, Ar*H*), 7.12 (1H, d, *J* = 7.5, COCH=C*H*); δ_C (75MHz, $CDCl_3$) 33.7, 44.3, 53.2, 56.3, 56.4, 60.8, 98.7, 110.2, 111.7, 118.5, 119.9, 124.3, 131.6, 134.5, 149.5, 149.9, 154.5, 190.9; HPLC (Daicel Chiralcel OD with 85:15 Hex:IPA) t_r = 38.3, 44.3 min; *m/z* (ES^+) 288.1594 ($[M+H]^+$ - $C_{17}H_{22}NO_3$ requires 288.1596) (CI^+) 288.2 [M+H] (100%).

2-(3,4-Dimethoxyphenyl)-1-(4-hydroxybutyl)-2,3-dihydropyridin-4(1H)-one 184



Purification by column chromatography (SiO_2, EtOAc) afforded the title compound as a yellow oil (55%), ν_{max}(neat)/cm^{-1} 3444 (OH), 1635 (C=O); δ_H (300MHz, $CDCl_3$) 1.36-1.69 (4H, m, 2 x CH_2), 1.78 (1H, br s, CH_2OH), 2.67 (1H, dd, *J* = 16.6, 8.7, PhCHCH_ACH_BCO), 2.82 (1H, dd, *J* = 16.6, 6.8, PhCHCH_ACH_BCO), 3.06 (2H, t, *J* = 7.5, NCH_2CH_2), 3.60 (2H, t, *J* = 6.0 CH_2CH_2OH), 3.86 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 4.55 (1H, dd, *J* = 8.7, 6.8, PhC*H*CH_ACH_BCO), 5.01 (1H, d, *J* = 7.5, COC*H*=CH), 6.83 (3H, m, ArH), 7.16 (1H, d, *J* = 7.5, COCH=C*H*); δ_C (75MHz, $CDCl_3$) 25.7, 29.9, 44.2, 53.7, 56.3, 61.0, 62.3, 98.2, 110.2, 111.6, 119.9, 131.5, 149.4, 149.8, 154.8, 191.02; *m/z* (ES^+) 306.1699 ($[M+H]^+$ - $C_{17}H_{24}NO_4$ requires 306.1700) (CI^+) 306.2 [M+H] (100%).

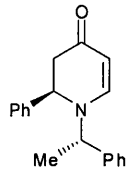
1-Benzyl-2-(furan-2-yl)-2,3-dihydropyridin-4(1H)-one 185



Purification by column chromatography (SiO_2, 60:40 EtOAc:PE) afforded the title compound as a brown oil (30%), ν_{max}(neat)/cm^{-1} 1666 (C=O); δ_H (300MHz, $CDCl_3$) 2.57 (1H, dd, *J* = 16.6, 6.0, PhCHCH_ACH_BCO), 2.66 (1H, dd, *J* = 16.6, 6.7,

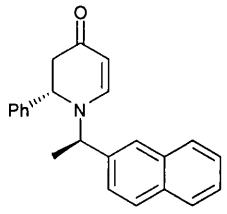
PhCHCH$_A$C*H*$_B$CO), 4.20-4.28 (2H, m, NC*H*$_2$Ph), 4.49 (1H, app t, *J* = 6.0, PhC*H*CH$_A$CH$_B$CO), 4.88 (1H, d, *J* = 7.5, COC*H*=CH), 6.09 (1H, d, *J* = 3.0, furyl), 6.18 (1H, dd, *J* = 3.0, 1.8, furyl), 6.32 (1H, dd, *J* = 3.3, 1.8, furyl), 7.08-7.30 (6H, m, COCH=C*H* + Ar*H*); δ_C (75MHz, $CDCl_3$) 40.2, 53.9, 58.3, 98.7, 109.2, 110.7, 128.2, 128.7, 129.3, 136.6, 143.1, 151.6, 153.1, 190.7; *m/z* (ES^+) 254.1178 ($[M+H]^+$ - $C_{16}H_{16}NO_2$ requires 254.1176) (CI^+) 254.1 [M+H] (100%).

2-Phenyl-1-(1-phenylethyl)-2,3-dihydropyridin-4(1H)-one 147[164]



The title compound was afforded as a crude mixture of diastereomers (7.6:2.4 *anti/syn*) (55%), (*R,S*): δ_H (300MHz, $CDCl_3$) 1.40 (1H, d, *J* = 6.8, C*H*$_3$), 2.63 (1H, dd, *J* = 16.2, 8.7, PhCHC*H*$_A$CH$_B$CO), 2.74 (1H, dd, *J* = 16.2, 6.8, PhCHCH$_A$C*H*$_B$CO), 4.32 (1H, d, *J* = 6.8, C*H*CH$_3$), 4.63 (1H, dd, *J* = 8.7, 6.8, PhC*H*CH$_A$CH$_B$CO), 4.97 (1H, d, *J* = 7.5, COC*H*=CH), 6.98 (1H, d, J = 7.5, COCH=C*H*), 7.19-7.35 (10H, m, Ar*H*), 7.24-7.40 (9H, m, Ar*H*); (*R,S*) and (*S,S*): δ_C (75MHz, $CDCl_3$) 19.8, 44.6, 53.7, 63.1, 99.3, 127.6, 128.4, 128.8, 129.1, 129.7, 136.7, 139.4, 153.6, 198.4; *m/z* (ES^+) 278.1539 ($[M+H]^+$ - $C_{19}H_{20}NO$ requires 278.1539) (CI^+) 278.2 [M+H] (100%).

1-(1-(Naphthalen-2-yl)ethyl)-2-phenyl-2,3-dihydropyridin-4(1H)-one 149

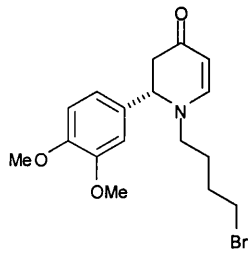


Product afforded crude as a mixture of diastereomers (8:2 *anti/syn*)without further purification (45%), ν_{max}(neat)/cm^{-1} 1638 (C=O); (*S,R*): δ_H (300MHz, $CDCl_3$) 1.21 (3H, d, *J* = 6.8, C*H*$_3$), 2.74 (1H, dd, *J* = 16.6, 8.7, PhCHC*H*$_A$CH$_B$CO), 2.84 (1H, dd, *J* = 16.2, 6.4, PhCHCH$_A$C*H*$_B$CO), 4.58 (1H, q, *J* = 6.8, C*H*CH$_3$), 4.73 (1H, dd, *J* = 8.7, 6.4, PhC*H*CH$_A$CH$_B$CO), 5.04 (1H, d, *J* = 7.5, COC*H*=CH), 7.27-7.65 (9H, m, Ar*H* +

COCH=C*H*), 7.73-95 (3H, m, Ar*H*); *m/z* (ES^+) 328.1692 ($[M+H]^+$ - $C_{23}H_{22}NO$ requires 328.1696) (CI^+) 328.3 [M+H] (50%).

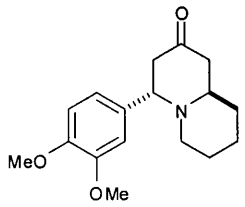
7.4 Synthesis of Lasubine (I) and Lasubine (II)

1-(4-Bromobutyl)-2-(3,4-dimethoxyphenyl)-2,3-dihydropyridin-4(1H)-one 215



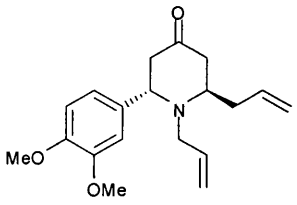
MsCl (0.095 ml, 1.24 mmol) and Hünig's base (0.307 ml, 1.78 mmol, 2 eq.) were added to a CH_2Cl_2 (20 ml) solution of pyridone **184** (272 mg, 0.89 mmol) at 0°C. Stirring was continued for 30 min. After extraction with water (30 ml) and solvent evaporation, the resulting complex was then dissolved in acetone (20 ml). LiBr 163 mg, 1.87 mmol) was added and stirring continued overnight. The reaction mixture was diluted with CH_2Cl_2 (30 ml) and washed with saturated $NaHCO_3$ and dried over $MgSO_4$. Evaporation of the solvent and purification by column chromatography (SiO_2, EtOAc) afforded the title compound as a yellow oil in 70% yield, ν_{max}(neat)/cm^{-1} 3444 (OH), 1660 (C=O); δ_H (300MHz, $CDCl_3$) 1.62-1.85 (4H, m, 2 x C*H*$_2$), 2.69 (1H, dd, *J* = 16.2, 9.0, PhCHC*H*$_A$CH$_B$CO), 2.81 (1H, dd, *J* = 16.2, 6.8, PhCHCH$_A$C*H*$_B$CO), 3.00-3.15 (2H, m, NC*H*$_2$CH$_2$), 3.30-3.40 (2H, m, CH$_2$C*H*$_2$Br), 3.87 (3H, s, OC*H*$_3$), 3.87 (3H, s, OC*H*$_3$), 4.55 (1H, dd, *J* = 9.0, 6.8, PhC*H*CH$_A$CH$_B$CO), 5.03 (1H, d, *J* = 7.5, COC*H*=CH), 6.84 (3H, s, Ar*H*), 7.13 (1H, d, *J* = 7.5, COCH=C*H*); δ_C (75MHz, $CDCl_3$) 26.2, 28.6, 43.0, 51.4, 51.6, 60.0, 68.0, 97.6, 108.7, 110.3, 122.8, 130.0, 148.0, 148.4, 153.0, 189.6; *m/z* (ES^+) 368.0851 ($[M+H]^+$ - $C_{17}H_{22}NO_3Br$ requires 368.0856) (CI^+) 368.1 [M+H] (100%).

trans-4-(3,4-Dimethoxyphenyl)hexahydro-1H-quinolizin-2(6H)-one 216a[147]



Dihydropyridone **215** (176 mg, 0.478 mmol) was dissolved in benzene (80 ml) and AIBN (10 mg) and tributyltin hydride (0.193 ml, 0.717 mmol) were added. The solution was heated to reflux and stirred for 2 h. The solution was cooled and the solvent removed in *vacuo*. The resulting yellow oil was dissolved in acetonitrile (25 ml) and washed with hexane (3 x 50 ml). The solvent was concentrated affording yellow oil (90%) as the racemic title compound in a 5:1 mixture of diastereoisomers. Column chromatography (65:35 hexane:acetone) afforded the major trans diastereomer, δ_H (300MHz, $CDCl_3$) 1.25-1.75 (6H, m), 2.11-2.42 (2H, m), 2.50-2.67 (2H, m), 2.81-2.97 (3H, m), 3.86(3H, s, OCH_3), 3.87 (3H, s, OCH_3), 4.22 (1H, dd, J = 6.4, 4.1), 6.58-6.64 (2H, m, Ar*H*), 6.71-6.77 (1H, m, Ar*H*); δ_C (75MHz, $CDCl_3$) 23.2, 23.8, 31.7, 46.6, 47.4, 51.1, 54.0, 55.6, 55.7, 63.7, 110.4, 111.5, 120.7, 125.3, 131.3, 148.2 148.5, 209.4; *m/z* (ES^+) 290.1753 ($[M+H]^+$ - $C_{17}H_{22}NO_3$ requires 290.1751) (CI^+) 290.1 [M+H] (100%).

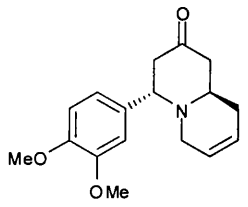
1,2-Diallyl-6-(3,4-dimethoxyphenyl)piperidin-4-one 217



To a round bottom flask flushed with nitrogen was dihydropyridone **182** (960 mg, 3.51 mmol) in THF (60 ml). $CuBr.SMe_2$ (2.13 g, 10.54mmol) was added followed by chlorotrimethylsilane (3.19 ml, 25.64 mmol) and the suspension cooled to – 78 °C. Allylmagnesium bromide (22.81ml, 22.81 mmol, 1.0 M solution in diethyl ether) was added dropwise and the mixture stirred for 4 h. The reaction mixture was poured into a 50:50 mixture of saturated NH_4Cl/NH_4OH 100ml. After stirring for 10 min the layers

were separated and the aqueous layer extracted with diethyl ether 3 x 50 ml. The combined organics were washed with brine (2 x 50 ml) then dried over $MgSO_4$ and the solvent removed *in vacuo* to afford a yellow oil. Purification by column chromatography (SiO_2, 85:15 PE:EtOAc) afforded the title compound as a yellow oil as a 1.5:1 mixture of diastereomers in 61% yield, ν_{max}(neat)/cm^{-1} 1651 (C=O); δ_H (300MHz, $CDCl_3$) 2.33-2.73 (6H, m, PhCHCH_2CO + CH_2CHCH_2CO + CH_2CH=CH_2), 2.96-3.18 (2H, m, NCH_2CH=CH_2), 3.34-3.44 (1H, m, NC*H*CH_2CO), 3.87 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 4.06 (1H, dd, J = 9.4, 4.5, PhC*H*$CH_A$$CH_B$CO), 5.02-5.26 (4H, m, 2 x CH=CH_2), 5.63-5.94 (2H, m, 2 x C*H*=CH_2), 6.81 (2H, s, Ar*H*), 6.96 (1H, s, Ar*H*); δ_C (75MHz, $CDCl_3$) 37.6, 41.8, 44.7, 48.8, 50.1, 54.0, 54.1, 54.2, 56.2, 58.4, 58.7, 62.6, 108.5, 108.7, 109.2, 115.6, 116.0, 116.5, 117.8, 118.2, 128.0, 131.3, 133.7, 134.8, 146.7, 147.6, 207.2, 207.5; *m/z* (ES^+) 316.1908 ($[M+H]^+$ - $C_{19}H_{25}NO_3$ requires 316.1907) (CI^+) 316.3 [M+H] (100%).

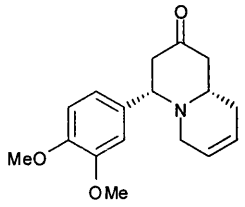
trans-4-(3,4-Dimethoxyphenyl)-3,4,9,9a-tetrahydro-1H-quinolizin-2(6H)-one 218a



To a round bottom flask flushed with nitrogen was added piperidinone **217** (285 mg, 0.999 mmol) dissolved in anhydrous CH_2Cl_2 (40 ml). To this was added second generation Grubbs catalyst (15 mg, 0.15 mmol) and the solution heated to reflux and stirred for 4 h. The reaction mixture was exposed to air, then concentrated. Purification by column chromatography (SiO_2, 50:50 PE:EtOAc) afforded the title compound as a yellow oil (44%), $[\alpha]_D^{25}$ = -3.5 (c 0.85, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1661 (C=O); δ_H (300MHz, $CDCl_3$) 1.84-2.14 (2H, m, CH=CHCH_2CH), 2.22-2.50 (2H, m, CHCH_2CO), 2.21 (1H, dd, J = 13.9, 10.2, PhCHC$H_A$$CH_B$CO), 2.80 (1H, dd, J = 13.9, 5.6, PhCHCH_ACH_BCO), 2.98 (1H, br d, J = 17.3, NC$H_A$$H_B$CH=CH), 3.28 (1H, br d, J = 17.3, NC$H_A$$H_B$CH=CH), 3.67 (1H, m, CH_2C*H*CH_2), 3.81 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 3.98 (1H, dd, J = 10.2, 5.6, PhC*H*$CH_A$$CH_B$CO), 5.41-5.50 (1H, m, NCH_2CH=C*H*CH_2), 5.66-5.75 (1H, m, NCH_2C*H*=CHCH_2), 6.75 (2H, m, Ar*H*), 6.86 (1H, s, Ar*H*); δ_C (75MHz, $CDCl_3$) 26.2, 47.0, 48.6, 49.5, 54.2, 56.3, 59.7, 110.4, 111.4,

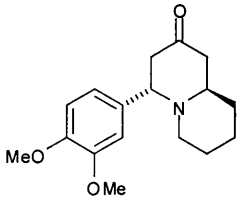
120.3, 124.6, 125.2, 135.1, 149.0, 149.8, 209.1; *m/z* (ES^+) 288.1592 ($[M+H]^+$ - $C_{17}H_{22}NO_3$ requires 288.1594) (CI^+) 288.2 [M+H] (100%).

cis-4-(3,4-Dimethoxyphenyl)-3,4,9,9a-tetrahydro-1H-quinolizin-2(6H)-one 218b



Following the same procedure for quinolizidine **218a**, the *cis* diastereomer was isolated following purification by column chromatography (SiO_2, 50:50 PE:EtOAc), which afforded the title compound as a yellow oil (33%), $[\alpha]_D^{25}$ = -45.7 (c 0.18, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1661 (C=O); δ_H (300MHz, $CDCl_3$) 2.18-2.22 (2H, m, CH=CHCH_2CH), 2.36-2.53 (4H, m, 2 x CH_2), 2.63-2.86 (2H, m, CH_2), 3.05-3.16 (1H, m, NCH_AH$_B$CH=CH), 3.30 (1H, dd, *J* = 12.3, 2.6, NCH$_A$$H_B$CH=CH), 3.87 (3H, s, OC$H_3$), 3.90 (3H, s, OC$H_3$), 5.52-5.61 (1H, m, NCH$_2$CH=C$HCH_2$), 5.66-5.74 (1H, m, NCH$_2CH$=CHCH$_2$), 6.79-6.96 (3H, m, Ar$H$); δ_C (75MHz, $CDCl_3$) 35.1, 48.6, 50.9, 52.5, 56.5, 58.5, 70.8, 110.3, 111.5, 120.0, 123.5, 125.4, 134.8, 149.0, 149.8, 207.7; *m/z* (ES^+) 288.1599 ($[M+H]^+$ - $C_{17}H_{22}NO_3$ requires 288.1594) (CI^+) 288.1 [M+H] (100%).

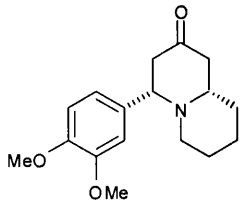
trans-4-(3,4-Dimethoxyphenyl)hexahydro-1H-quinolizin-2(6H)-one 216a[147]



Quinolizidine **218a** (77 mg, 0.26 mmol) was dissolved in methanol (10 ml) and Pd/C (50 mg) added. The suspension was stirred under a H_2 atmosphere for 18 h then filtered through Celite and concentrated to afford a yellow oil. Purification by column chromatography (SiO_2, 65:35 hexane:acetone) afforded the title compound as a colourless oil (90%), $[\alpha]_D^{25}$ = -5.0 (c 0.40, $CHCl_3$); δ_H (300MHz, $CDCl_3$) 1.25-1.75 (6H, m), 2.11-2.42 (2H, m), 2.50-2.67 (2H, m), 2.81-2.97 (3H, m), 3.86(3H, s, OCH_3), 3.87 (3H, s, OCH_3), 4.22 (1H, dd, *J* = 6.4, 4.1), 6.58-6.64 (2H, m, ArH), 6.71-6.77 (1H, m,

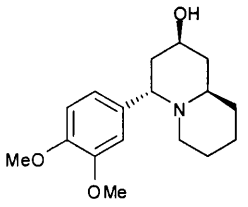
Ar*H*); δ_C (75MHz, $CDCl_3$) 23.2, 23.8, 31.7, 46.6, 47.4, 51.1, 54.0, 55.6, 55.7, 63.7, 110.4, 111.5, 120.7, 125.3, 131.3, 148.2 148.5, 209.4; *m/z* (ES^+) 290.1753 ($[M+H]^+$ - $C_{17}H_{22}NO_3$ requires 290.1751) (CI^+) 290.1 [M+H] (100%).

cis-4-(3,4-Dimethoxyphenyl)hexahydro-1H-quinolizin-2(6H)-one 216b[148]



Quinolizidine **218b** (103 mg, 0.36 mmol) was dissolved in methanol (12 ml) and Pd/C (55 mg) added. The suspension was stirred under a H_2 atmosphere for 18 h then filtered through Celite and concentrated to afford a yellow oil. Purification by column chromatography (SiO_2, 70:30 EtOAc:hexane) afforded the title compound as a colourless oil (91%), $[\alpha]_D^{25}$ = -25.0 (c 0.32, $CHCl_3$); δ_H (300MHz, $CDCl_3$) 1.24-1.75 (7H, m), 2.19-2.50 (4H, m), 2.64 (1H, t, *J* = 12.8), 2.73 (1H, d, *J* = 11.4), 3.15 (1H, dd, *J* = 12.1, 3.1), 3.82 (3H, s, OCH_3), 3.85 (1H, s, OCH_3), 6.75 (2H, m, Ar*H*), 6.93 (1H, br s, Ar*H*); δ_C (75MHz, $CDCl_3$) 24.6, 26.3, 34.8, 49.2, 51.3, 53.2, 56.3, 56.4, 62.9, 70.4, 110.2, 111.5, 119.9, 135.6, 148.8, 149.8, 208.2; *m/z* (ES^+) 290.1753 ($[M+H]^+$ - $C_{17}H_{22}NO_3$ requires 290.1751) (CI^+) 290.1 [M+H] (100%).

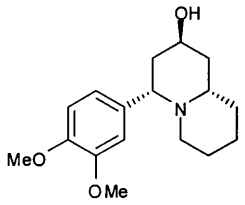
Lasubine (I) 199[147]



To a solution of quinolizidine **216a** (32 mg, 0.107 mmol) in anhydrous THF (5 ml) at -78 °C under nitrogen was added L-Selecride (0.164 ml, 0.164 mmol, 1M solution in THF). The reaction mixture was stirred for 2 h at – 78 °C, then it was warmed to 0 °C and water (3 ml) added. The mixture was concentrated and saturated $NaHCO_3$ (5 ml) was added. The aqueous layer was extracted with $CHCl_3$ (3 x 5 ml). The organic layer was dried over $MgSO_4$, and the solvent removed *in vacuo*. Purification by column

chromatography (SiO_2, 80:20 EtOAc:MeOH) afforded the title compound as a colourless oil in 78% yield, $[\alpha]_D^{25}$ = -4.0 (c 0.50, MeOH), for 65% ee (lit., $[\alpha]_D^{25}$ = -7.0 (c 0.4, MeOH); δ_H (300MHz, $CDCl_3$) 1.18-2.16 (11H, m), 2.24 (1H, m), 2.74 (1H, m), 2.96 (1H, m), 3.84 (3H, s, OC*H*$_3$), 3.86 (3H, s, OC*H*$_3$), 4.18 (1H, hept, *J* = 4.4), 6.77-6.89 (3H, m, Ar*H*); δ_C (75MHz, $CDCl_3$) 23.7, 27.4, 37.9, 48.7, 52.8, 53.9, 54.1, 62.9, 66.0, 108.8, 109.7, 118.7, 146.22, 147.0; *m/z* (ES^+) 292.1907 ($[M+H]^+$ - $C_{17}H_{26}NO_3$ requires 292.1907) (CI^+) 292.2 [M+H] (100%).

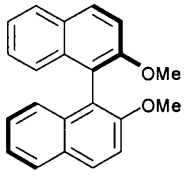
Lasubine (II) 219[148]



To a solution of quinolizidine **216b** (28 mg, 0.097 mmol) in anhydrous THF (4 ml) at – 78 °C under nitrogen was added LS-Selectride (0.120 ml, 0.120 mmol, 1M solution in THF). The reaction mixture was stirred for 12 h at – 78 °C, then it was warmed to 0°C and water added (3 ml). The mixture was concentrated and saturated $NaHCO_3$ was added. The aqueous layer was extracted with $CHCl_3$ (3 x 5 ml). The organics were dried over $MgSO_4$, and the solvent removed *in vacuo*. Purification by column chromatography (SiO_2, 80:20 $CHCl_3$:MeOH) afforded the title compound as a colourless oil (77%), $[\alpha]_D^{25}$ = -13 (c 0.35, MeOH), for 48% ee (lit., $[\alpha]_D^{25}$ = -37.7 (c 0.32, MeOH); δ_H (300MHz, $CDCl_3$) 1.15-2.06 (12H, m), 2.39 (1H, m), 2.69 (1H, d, *J* = 11.5), 3.32 (1H, br d, *J* = 10.9), 3.86 (3H, s, OC*H*$_3$), 3.88 (3H, s, OC*H*$_3$), 4.15 (1H, t, *J* = 2.7), 6.75-6.95 (3H, m, Ar*H*); δ_C (75MHz, $CDCl_3$) 25.2, 26.5, 33.9, 40.7, 43.1, 53.6, 56.2, 56.4, 56.9, 63.9, 65.5, 110.8, 111.2, 120.1, 137.5, 148.2, 149.4; *m/z* (ES^+) 292.1907 ($[M+H]^+$ - $C_{17}H_{26}NO_3$ requires 292.1907) (CI^+) 292.2 [M+H] (100%).

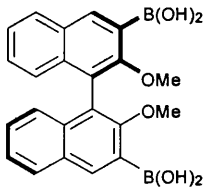
7.5 Preparation of modified BINOL ligands

(*R*)-2,2'-Dimethoxy-1,1'-binaphthyl 144[165]



A suspension of (*R*)-BINOL (1.89 g, 6.6 mmol) was heated in 25ml of acetone to give a homogeneous solution. To this solution stirred under N_2 was added (2.73 g, 19.8 mmol) of K_2CO_3 followed by (2.81 g, 19.8 mmol) of CH_3I, and the mixture was refluxed for 24 h. The solvent was evaporated to leave a yellow solid that was washed with water, and dried under vacuum to give a white solid (2.08 g 100%), mp 227-229 °C (lit., 224-225 °C); $[\alpha]_D^{25}$ = +73.4 (c 1.2, THF) (lit., $[\alpha]_D^{25}$ = -72.8 (c 1.2, THF); δ_H (300MHz, $CDCl_3$) 3.68 (6H, s, 2 x OC*H*$_3$), 7.02 (2H, m, Ar*H*), 7.09-7.28 (4H, m, Ar*H*), 7.38 (2H, m, Ar*H*), 7.79 (2H, m, Ar*H*), 7.88 (2H, s, Ar*H*); δ_C (75MHz, $CDCl_3$) 57.3, 77.0, 77.5, 78.9, 114.6, 119.9, 123.9, 125.7, 126.7, 128.4, 129.6, 129.8, 134.4, 155.4.

(*R*)-2,2'-Dimethoxy-1,1'-binaphthyl-3,3'-diyldiboronic acid 145[126]



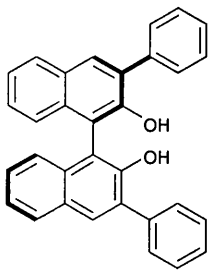
To a round bottom flask flushed with N_2 were placed dry Et_2O (300 ml) and TMEDA (6.3 g, 54 mmol). To this solution was added *n*-BuLi (35 ml, 56 mmol, 1.6 M in hexane). The solution was stirred for 30 min at room temperature, solid (*R*)-**144** (5.9 g, 19 mmol) was added in one portion, and the reaction mixture was stirred for 3 h. The resulting light brown suspension was cooled to - 78 °C, and $B(OEt)_3$ (17.1 g, 117 mmol) was added via syringe over a period of 10 min. The solution was allowed to warm to room temperature and was left stirring overnight. The reaction mixture was cooled to 0 °C, 1 M HCl (150 ml) was added, and the reaction mixture was stirred for 2 h. The phases were separated, and the organic phase was washed twice with 1 M HCl (100 ml)

and saturated aqueous NaCl (100 ml) and then dried over $MgSO_4$ and the solvent removed *in vacuo*. Recrystalisation from toluene afforded the title compound as a white solid in 80% yield, mp >250 °C (lit., >250 °C); $[\alpha]_D^{25}$ = -149.4 (c 1.0, $CHCl_3$) (lit., $[\alpha]_D^{25}$ = -153.4 (c 1.0, $CHCl_3$); δ_H (300MHz, acetone-d_6) 3.41 (6H, s, 2 x OC*H*$_3$), 7.10 (2H, m, Ar*H*), 7.30-7.37 (2H, m, Ar*H*), 7.42-7.49 (2H, m, Ar*H*), 8.02-8.06 (2H, m, Ar*H*), 8.55 (2H, br s, Ar*H*); δ_C (75MHz, acetone-d_6) 62.2, 124.2, 126.1, 126.7, 128.6, 130.1, 131.8, 137.0, 161.7; δ_B (96MHz, acetone-d_6) 29.9.

7.5.1 General procedure for the Suzuki cross-coupling reaction

In a 50 ml two-necked flask equipped with a condenser were placed (*R*)-**145** (0.75 g, 1,9 mmol), $Ba(OH)_2.8H_2O$ (1.74 g, 5.5 mmol), and $Pd(PPh_3)_4$ (0.116 g, 0.1 mmol), and the flask was evacuated and filled with N_2 three times. 1,4-Dioxane (12 ml), H_2O (4 ml), and the appropriate bromoarene (6.0 mmol) were added. The reaction mixture was refluxed for 24 h under N_2, and cooled to room temperature. The dioxane was removed at reduced pressure, and the resulting phase was redissolved in CH_2Cl_2 (75 ml), washed with 1 M HCl (2 x 50 ml) and saturated aqueous NaCl (75 ml), and dried over $MgSO_4$. The solvent was removed to give the crude product as a yellow semicrystalline oil. The crude product was dissolved in dry CH_2Cl_2 (75 ml) and cooled to 0 °C, BBr_3 (1 ml) was added over a period of 10 min, and the reaction mixture was stirred for 18 h at room temperature. The pale yellow solution was cooled to 0 °C, and H_2O (150 ml) was carefully added. The phases were separated, and the organic phase was washed with H_2O (2 x 100 ml) and brine (100 ml), dried over $MgSO_4$, and concentrated. The resulting yellow solid was chromatographed on silica to give the following BINOL type ligands.

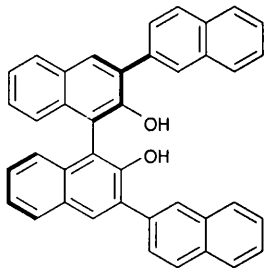
(*R*)-3,3'-Diphenyl-1,1'-binaphthyl-2,2'-diol 146a[126]



Purification by column chromatography (SiO_2, 95:5 PE:EtOAc) afforded the title compound as a white solid (68%), mp 197–199 °C (lit., 200–202 °C); $[\alpha]_D^{25}$ = -106.0 (c

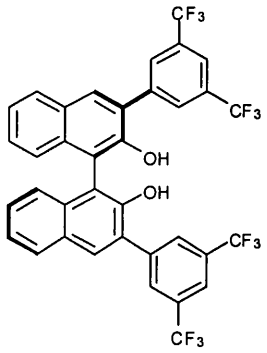
0.75, THF) (lit., $[\alpha]_D^{25}$ = 135.0 (c 1.0, THF); δ_H (300MHz, $CDCl_3$) 5.36 (2H, s, 2 x O*H*), 7.18-7.25 (2H, m, Ar*H*), 7.26-7.51 (10H, m, Ar*H*), 7.69-7.76 (4H, m, Ar*H*), 7.87-7.93 (2H, m, Ar*H*), 8.00 (2H, br s, Ar*H*); δ_C (75MHz, $CDCl_3$) 112.8, 124.7, 124.8, 127.8, 128.2, 128.9, 129.9, 130.0, 131.1, 131.8, 133.4, 137.8, 150.6.

(*R*)-3,3′-Bis(2-naphthyl)-2,2′-dihydroxy-1,1′-dinaphthyl 146b[166]



Purification by column chromatography (SiO_2, 95:5 PE:EtOAc) afforded the title compound as a white solid (65%), mp 247–249 °C (lit., 184-185 °C); $[\alpha]_D^{25}$ = -33.0 (c 1.0, THF) (lit., $[\alpha]_D^{25}$ = -32.9 (c 1.0, THF); δ_H (300MHz, $CDCl_3$) 5.53 (2H, br s, 2 x O*H*), 7.29-7.47 (10H, m, Ar*H*), 7.50-7.57 (4H, m, Ar*H*), 7.87-8.00 (10H, m, Ar*H*), 8.16 (2H, br s, Ar*H*), 8.24 (2H, br s, Ar*H*); δ_C (75MHz, $CDCl_3$) 112.9, 124.8, 124.8, 126.7, 126.7, 127.9, 128.1, 128.4, 128.7. 128.9, 130.0, 131.1, 132.1, 133.2, 133.5, 133.9, 135.5, 150.8.

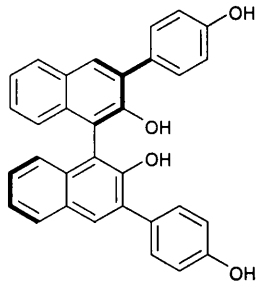
(*R*)-3,3'-bis(3,5-bis(Trifluoromethyl)phenyl)-1,1'-binaphthyl-2,2'-diol 146c[166]



Purification by column chromatography (SiO_2, 95:5 PE:EtOAc) afforded the title compound as a white solid (60%), mp 101-103 °C (lit., 97-99 °C); $[\alpha]_D^{25}$ = -11.6 (c 1.1, THF) (lit., $[\alpha]_D^{25}$ = -11.9 (c 1.1, THF); δ_H (300MHz, $CDCl_3$) 5.27 (2H, s, 2 x O*H*), 7.16-7.25 (2H, m, Ar*H*), 7.32-7.51 (4H, m, Ar*H*), 7.86-7.99 (4H, m, Ar*H*), 8.09 (2H, br s,

Ar*H*), 8.21 (4H, br s, Ar*H*); δ_C (75MHz, $CDCl_3$) 112.2, 121.7, 124.4, 125.7, 128.1, 129.1, 129.3, 129.9, 130.3, 131.8, 132.2, 132.7, 132.8, 133.7, 139.9, 150.3.

(*R*)-3,3'-bis(4-Hydroxyphenyl)-1,1'-binaphthyl-2,2'-diol 147d



Purification by column chromatography (SiO_2, 60:40 PE:EtOAc) afforded the title compound as a white solid (45%), mp 142–144 °C; $[\alpha]_D^{25}$ = +57.0 (c 1.0, THF); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3514 (OH), 3582 (OH); δ_H (300MHz, $CDCl_3$) 5.41 (2H, s, 2 x O*H*), 5.89 (2H, br s, 2 x O*H*), 6.90-6.98 (4H, m, Ar*H*), 7.14-7.41 (6H, m, Ar*H*), 7.55-7.65 (4H, m, Ar*H*), 7.86-7.92 (2H, m, Ar*H*), 7.96 (2H, s, Ar*H*); δ_C (75MHz, $CDCl_3$) 112.9, 115.8, 124.7, 128.7, 129.9, 130.0, 130.7, 131.3, 131.3, 133.2, 150.6, 156.1; *m/z* (ES^+) 488.1856 ($[M+NH_4]^+$ - $C_{32}H_{26}NO_4$ requires 488.1856) (CI^+) 488.2 $[M+NH_4]$ (100%).

7.6 Preparation of BINOL propeller boronate 117

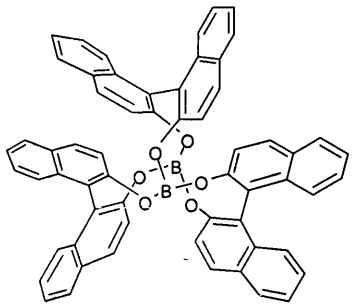
7.6.1 Synthesis of 117 from BINOL and $B(OMe)_3$

To a round bottom flask flushed with nitrogen was added (*R*)-BINOL (330 mg, 1.15 mmol) dissolved in $CDCl_3$ or CH_2Cl_2. To this solution was then added trimethyl borate, and the solution refluxed using Dean-Stark apparatus containing 4Å molecular sieves (beads) in the side arm of the Dean-Stark for 48 h. The compound was used as a solution in either $CDCl_3$ or CH_2Cl_2.

7.6.1 Synthesis of 117 from BINOL and $BH_3.SMe_2$

Borane-dimethyl sulfide (0.2 ml, 2.0 mmol) is added dropwise to a cooled (0 °C) solution of (*R*)-BINOL (858 mg, 3.0 mmol) in $CDCl_3$ or CH_2Cl_2 (30 ml). The solution was allowed to warm up to room temperature and was stirred for 14 h. The compound was used as a solution in $CDCl_3$ or CH_2Cl_2. The product was formed in 100% conversion

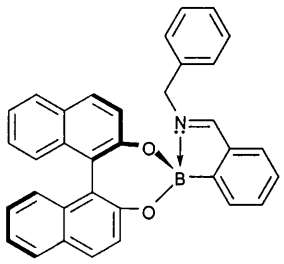
Hexanaphthohexaoxa-1,8-diborabicyclo[6.6.6]-eicosa-3,5,10,12,16,18-hexaene 117[100]



Product formed as a solution in $CDCl_3$, δ_H (300MHz, $CDCl_3$) 6.53 (2H, d, *J* = 9.0 Ar*H*), 6.58 (2H, d, *J* = 9.0 Ar*H*) 6.94 (2H, d, *J* = 8.3 Ar*H*), 7.15 (2H, dd, *J* = 8.3, 6.7, Ar*H*), 7.36 (2H, dd, *J* = 8.3, 6.7, Ar*H*), 7.63 (2H, d, *J* = 7.9, Ar*H*); δ_C (75MHz, $CDCl_3$) 120.7, 124.3, 125.4, 125.8, 127.7, 128.0, 130.1, 133.5, 148.2; δ_B (96MHz, $CDCl_3$) 15.9.

7.7 Preparation of intramolecular boron-BINOL compounds

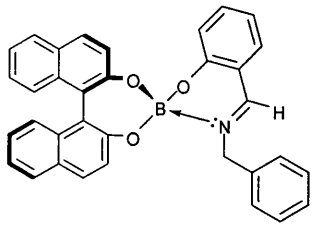
(*R*,*E*)-N-(2-Naphtho[15,10,1,2-def][1,3,2]dioxaborepin-4-yl)benzylidene)(phenyl)methanamine 136



To a solution of (*R*)-BINOL (497 mg, 1.74 mmol) and 2-formyl benzeneboronic acid (260 mg, 1.74 mmol) in THF (8 ml) was added benzylamine dropwise. The mixture was stirred for 24 h then the solvent removed in vacuo to yield an orange solid, which was then recrystalised from CH_2Cl_2 / hexane to afford the title compound as a yellow solid (87%), mp 155 °C (dec); $[\alpha]_D^{25}$ = -481.0 (c 1.0, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 1631 (C=N); δ_H (300MHz, $CDCl_3$) 4.61 (2H, d, *J* = 1.5, CH_2Ph), 7.04 (1H, m, Ar*H*), 7.18-7.53 (16H, m, Ar*H*), 7.84-7.99 (5H, m, Ar*H* + C*H*N); δ_C (75MHz, $CDCl_3$) 53.9, 123.3,

123.5, 123.8, 125.7, 125.8, 127.5, 127.6, 128.2, 128.4, 128.5, 129.3, 129.4, 129.5, 129.8, 130.6, 137.3, 154.7, 168.8; δ_B (96MHz, $CDCl_3$) 14.1; *m/z* (ES^+) 490.1979 ($[M+H]^+$ - $C_{34}H_{25}BNO_2$ requires 490.1973) (CI^+) 490.3 [M+H] (100%).

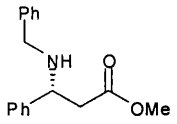
(*R*,*E*)-N-(2-(Dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaborepin-4-yloxy)benzylidene)-1-phenylmethanamine 137



To a round bottom flask flushed with nitrogen was added (*R*)-BINOL (352 mg, 1.23 mmol) dissolved in anhydrous THF (20 ml). Salicylic aldehyde (0.131 ml, 1.23 mmol) was then added, followed by benzylimine (0.134 ml, 1.23 mmol) and $B(OMe)_3$. The reaction mixture was heated to reflux with a Dean-Stark apparatus and stirred for 18 h. Then the solvent was removed to afford an orange powder. Recrystalisation from CH_2Cl_2 afforded the title compound as a yellow solid (80%), mp 147 °C (dec); $[\alpha]_D^{25}$ = -32.2 (c 0.25, $CHCl_3$); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 1644 (C=N); δ_H (300MHz, $CDCl_3$) 4.42 (1H, d, *J* = 16.2, C*H*$_A$H$_B$Ph), 4.64 (1H, d, *J* = 16.2, CH$_A$*H*$_B$Ph), 6.78-6.96 (2H, m, Ar*H*), 7.01-7.48 (15H, m, Ar*H*), 7.69-7.84 (5H, m, Ar*H* + C*H*N); δ_C (75MHz, $CDCl_3$) 55.3, 111.3, 116.1, 118.2, 118.9, 119.7, 124.4, 124.6, 127.9, 128.2, 128.8, 129.1, 129.6, 129.8, 130.9, 131.6, 131.8, 133.8, 134.5, 137.2, 153.1, 160.3, 161.8; δ_B (96MHz, $CDCl_3$) 5.98; *m/z* (ES^+) 506.1921 ($[M+H]^+$ - $C_{34}H_{25}BNO_3$ requires 506.1922) (CI^+) 506.2 [M+H] (100%).

7.8 Boron-BINOL mediated Mannich type reaction

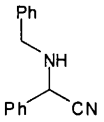
(*R*)-Methyl 3-(benzylamino)-3-phenylpropanoate 191[122]



To a suspension of powdered 4Å molecular sieves (1.0g) in CH_2Cl_2 were added (*R*)-BINOL (120mg, 0.41 mmol) and triphenyl borate (61 mg, 0.21 mmol) at room temperature under nitrogen. After stirring for 1 h, the mixture was cooled to 0 °C, then a solution of Benzylidenebenzylamine (41 mg, 0.21 mmol) in CH_2Cl_2 (1 ml) was added dropwise. After stirring at the same temperature for 10 min, the mixture was cooled to -78 °C, and a solution of tert-Butyl-(1-methoxy-vinyloxy)-dimethyl-silane (0.061ml, 0.21 mmol) in CH_2Cl_2 (1 ml) was added dropwise. After stirring for 5 h, the solution was washed with water (3 x 30 ml) and saturated $NaHCO_3$ (2 x 30 ml), and then dried over $MgSO_4$. Evaporation of solvent and purification by column chromatography (SiO_2, 60:40 PE: EtOAc) afforded the title compound as a yellow oil in 40% yield, δ_H (300MHz, $CDCl_3$) 2.54 (1H, dd, J = 15.4, 5.3, $CHCH_ACH_BCO$), 2.68 (1H, dd, J = 15.4, 8.7, $CHCH_ACH_BCO$), 3.44 (1H, d, J = 13.2, CH_ACH_BPh), 3.55 (3H, s, OCH_3), 3.57 (1H, d, J = 13.2, CH_ACH_BPh), 4.03 (1H, dd, J = 8.7, 5.3, $NCHPhCH_2$), 7.13-7.34 (10H, m, Ar*H*); δ_C (75MHz, $CDCl_3$) 42.9, 51.3, 51.4, 58.7, 126.6, 127.0, 127.5, 128.1, 128.3, 128.6, 140.3, 142.6, 172.2; HPLC (Daicel Chiralcel OD-H with 98:2 Hex:IPA, flow rate = 0.5 ml/min) t_r = 16.9, 28.9 min.

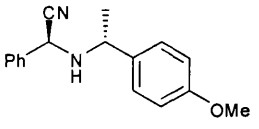
7.9 Boron-BINOL mediated Strecker reactions

2-(Benzylamino)-2-phenylacetonitrile 188[132]



To a suspension of powdered 4Å molecular sieves (1.0g) in CH_2Cl_2 were added (*R*)-BINOL (300mg, 1.05 mmol) and triphenyl borate (61 mg, 0.21 mmol) at room temperature under nitrogen. After stirring for 1 h, the mixture was cooled to 0 °C, then a solution of Benzylidenebenzylamine (41 mg, 0.21 mmol) in CH_2Cl_2 (1 ml) was added dropwise. After stirring at the same temperature for 10 min, the mixture was cooled to – 78 °C, and trimethyl silyl cyanide (0.028ml, 0.21 mmol) was added dropwise. After stirring for 5 h, the solution was washed with water (3x 30 ml) and saturated $NaHCO_3$ (2 x 30 ml), and then dried over $MgSO_4$. The solvent was removed *in vacuo* and purification by column chromatography (SiO_2, 90:10 PE: EtOAc) afforded the title compound as a clear oil in 63% yield, δ_H (300MHz, $CDCl_3$) 3.88 (1H, d, J = 12.8, C*H*$_A$CH$_B$Ph), 3.99 (1H, d, J = 12.8, CH$_A$C*H*$_B$Ph), 4.68 (1H, s, NHC*H*PhCN), 6.73 (1H, m, Ar*H*) 7.11-7.38 (7H, m, Ar*H*), 7.42-7.50 (2H, m, Ar*H*); δ_C (75MHz, $CDCl_3$) 51.7, 53.8, 119.2, 128.1, 128.9, 129.1, 129.5, 130.0, 135.2, 138.5, 143.5.

(*S*)-2-((*R*)-1-(4-Methoxyphenyl)ethylamino)-2-phenylacetonitrile 190[133]

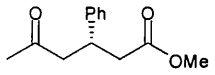


To a suspension of powdered 4Å molecular sieves (1.0g) in CH_2Cl_2 were added (*R*)-BINOL (300mg, 1.05 mmol) and triphenyl borate (61 mg, 0.21 mmol) at room temperature under nitrogen. After stirring for 1 h, the mixture was cooled to 0 °C, then a solution of (*R*,*E*)-N-benzylidene-1-(4-methoxyphenyl)ethanamine (50 mg, 0.21 mmol) in CH_2Cl_2 (1 ml) was added dropwise. After stirring at the same temperature for 10 min, the mixture was cooled to – 78 °C, and trimethyl silyl cyanide (0.028ml, 0.21 mmol) was added dropwise. After stirring for 5 h, the solution was washed with water (3x 30 ml) and saturated $NaHCO_3$ (2 x 30 ml), and then dried over $MgSO_4$. The solvent

was removed *in vacuo*. The compound was afforded as a crude mixture of diastereomers (27% de) without further purification (60%), (major diastereomer) δ_H (300MHz, $CDCl_3$) 1.52 (3H, d, J = 6.7, CH_3), 3.71 (3H, s, OCH_3), 4.09 (1H, q, J = 6.7, $CHCH_3$), 4.28 (1H, s, NHC*H*PhCN), 6.74-6.86 (2H, m, Ar*H*) 7.02-7.42 (7H, m, Ar*H*).

7.10 Boron-BINOL mediated conjugate addition reaction

(*S*)-Methyl 5-oxo-3-phenylhexanoate 193[167]



To a suspension of powdered 4Å molecular sieves (1.0g) in CH_2Cl_2 were added (*R*)-BINOL (145mg, 0.51 mmol) and trimethyl borate (0.28 ml, 0.25 mmol) at room temperature under nitrogen. After stirring for 1 h, the mixture was cooled to 0 °C, then a solution of *trans*-4-phenyl-3-buten-2-one (41 mg, 0.21 mmol) in CH_2Cl_2 (1 ml) was added dropwise. After stirring at the same temperature for 10 min, the mixture was cooled to – 78 °C, and a solution of tert-Butyl-(1-methoxy-vinyloxy)-dimethyl-silane (0.055ml, 0.25 mmol) in CH_2Cl_2 (1 ml) was added dropwise. After stirring for 5 h, the solution was washed with water and saturated $NaHCO_3$, and then dried over $MgSO_4$. Evaporation of solvent and purification by column chromatography (SiO_2, 95:5 PE: EtOAc) afforded the title compound as a yellow solid (54%), mp 39-41 °C; $[\alpha]_D^{25}$ = -3.04 (c 2.0, benzene) (lit., $[\alpha]_D^{25}$ = -16.9 (c 1.2, benzene); δ_H (300MHz, $CDCl_3$) 2.06 (3H, s, CH_3CO), 2.60 (1H, dd, J = 15.4, 7.5, $CHCH_ACH_BCO$), 2.68 (1H, dd, J = 15.4, 7.2, $CHCH_ACH_BCO$), 2.78 (1H, dd, J = 16,9, 7.5, $CHCH_ACH_BCO$), 2.86 (1H, dd, J = 16.6, 6.8, $CHCH_ACH_BCO$), 3.58 (3H, s, OCH_3), 3.67 (1H, app quin, J = 7.5, CH_2CHCH_2), 7.16-7.36 (5H, m, Ar*H*); δ_C (75MHz, $CDCl_3$) 30.3, 35.6, 37.6, 49.8, 52.0, 124.4, 124.6, 127.9, 142.8, 181.8, 204.8; *m/z* (CI^+) 238.1 [M+NH_4] (100%).

8 List of References

(1) Wynn, R. L.; Blake, D. A., *Teratology*, 1970, ***3***, 211-213.
(2) Davies, E. F.; Avery, G. S., *Drugs*, 1971, ***2***, 416-426.
(3) Nicolaou, K. C.; Vourloumis, D.; Winssinger, N.; Baran, P. S., *Angew. Chem., Int. Ed. Engl.*, 2000, ***39***, 44-122.
(4) Sheehan, J. C.; Henery-Logan, K. R., *J. Am. Chem. Soc*, 1959, ***81***, 3089-3094.
(5) Nicolaou, K. C.; Yang, Z.; Liu, J. J.; Ueno, H.; Nantermet, P. G.; Guy, R. K.; Claiborne, C. F.; Renaud, J.; Couladouros, E. A.; Paulvannan, K.; Sorensen, E. J., *Nature*, 1994, ***367***, 630-634.
(6) Stead, P.; Marley, H.; Mahmoudian, M.; Webb, G.; Noble, D.; Ip, Y. T.; Piga, E.; Rossi, T.; Roberts, S.; Dawson, M. J., *Tetrahedron: Asymmetry*, 1996, ***7***, 2247-2250.
(7) Black, P.; Jenkins, K.; Williams, J. M. J., *Tetrahedron: Asymmetry*, 2002, ***13***, 317.
(8) Noyori, R.; Ikeda, T.; Ohkuma, T.; Widhalm, M.; Kitamura, M.; Takaya, H.; Akutagawa, S.; Sayo, N.; Saito, T.; Taketomi, T.; Kumobayashi, H., *J. Am. Chem. Soc.*, 1989, ***111***, 9134-9135.
(9) Keil, O.; Schneider, M. P.; Rasor, J. P., *Tetrahedron: Asymmetry*, 1995, ***6***, 1257-1260.
(10) Imai, T.; Tamura, T.; Yamamuro, A.; Sato, T.; Wollmann, T. A.; Kennedy, R. M.; Masamune, S., *J. Am. Chem. Soc.*, 1986, ***108***, 7402-7404.
(11) Brown, H. C.; Jadhav, P. K., *Tetrahedron Lett.*, 1984, ***25***, 1215-1218.
(12) Evans, D. A.; Ennis, M. D.; Mathre, D. J., *J. Am. Chem. Soc.*, 1982, ***104***, 1737-1739.
(13) Dalko, P. I.; Moisan, L., *Angew. Chem.-Int. Edit.*, 2001, ***40***, 3726-3748.
(14) Procter, G. *Stereoselectivity in Organic Synthesis*; OUP: New York, 1998.
(15) Kitamura, M.; Suga, S.; Kawai, K.; Noyori, R., *J. Am. Chem. Soc*, 1986, ***108***, 6071-6072.
(16) Katsuki, T.; Sharpless, K. B., *J. Am. Chem. Soc*, 1980, ***102***, 5974-5976.
(17) Handy, S. T., *Curr. Org. Chem.*, 2000, ***4***, 363-395.
(18) Takamura, M.; Hamashima, Y.; Usuda, H.; Kanai, M.; Shibasaki, M., *Angew. Chem., Int. Ed.*, 2000, ***39***, 1650-1652.
(19) Pearlman, B. A., *J. Am. Chem. Soc.*, 1979, ***101***, 6404-6408.
(20) Govindac.Tr; Rajagopa.Tg; Viswanat.N, *J. Chem. Soc., Perkin Trans. 1*, 1974, 1161-1165.
(21) Hedges, S. H.; Herbert, R. B.; Wormald, P. C., *J. Nat. Prod.*, 1993, ***56***, 1259-1267.
(22) Jorgensen, K. A., *Angew. Chem., Int. Ed. Engl.*, 2000, ***39***, 3558-3588.
(23) Hattori, K.; Yamamoto, H., *J. Org. Chem.*, 1992, ***57***, 3264-3265.
(24) Hattori, K.; Yamamoto, H., *Tetrahedron*, 1993, ***49***, 1749-1760.
(25) Ishihara, K.; Yamamoto, H., *J. Am. Chem. Soc.*, 1994, ***116***, 1561-1562.
(26) Cros, J. P.; Perez-Fuertes, Y.; Thatcher, M. J.; Arimori, S.; Bull, S. D.; James, T. D., *Tetrahedron: Asymmetry*, 2003, ***14***, 1965-1968.
(27) Danishefsky, S., *J. Am. Chem. Soc.*, 1974, ***96***, 7807-7808.
(28) Hermitage, S.; Jay, D. A.; Whiting, A., *Tetrahedron Lett.*, 2002, ***43***, 9633-9636.
(29) Whiting, A.; Windsor, C. M., *Tetrahedron*, 1998, ***54***, 6035-6050.

(30) Hermitage, S.; Howard, J. A. K.; Jay, D.; Pritchard, R. G.; Probert, M. R.; Whiting, A., *Org. Biomol. Chem.*, 2004, **2**, 2451-2460.
(31) Di Bari, L.; Guillarme, S.; Hermitage, S.; Howard, J. A. K.; Jay, D. A.; Pescitelli, G.; Whiting, A.; Yufit, D. S., *Synlett.*, 2004, 708-710.
(32) Yuan, Y.; Li, X.; Ding, K. L., *Org. Lett.*, 2002, **4**, 3309-3311.
(33) Ali, T.; Chauhan, K. K.; Frost, C. G., *Tetrahedron Lett.*, 1999, **40**, 5621-5624.
(34) Patmore, N. J.; Hague, C.; Cotgreave, J. H.; Mahon, M. F.; Frost, C. G.; Weller, A. S., *Chem. Eur. J.*, 2002, **8**, 2088-2098.
(35) Xiao, D. J.; Wang, L. J.; Feng, X. M., *Synlett.*, 2005, 1531-1534.
(36) Cheng, K.; Zeng, B. Q.; Yu, Z. P.; Gao, B.; Feng, X. M., *Synlett.*, 2005, 1018-1020.
(37) Jaber, N.; Fiaud, J. C.; Collin, J., *Tetrahedron Lett.*, 2001, **42**, 9157-9159.
(38) Bull, S. D.; Davidson, M. G.; Johnson, A. L.; Robinson, D.; Mahon, M. F., 2003, 1750-1751.
(39) Kuethe, J. T.; Wong, A.; Davies, I. W.; Reider, P. J., *Tetrahedron Lett.*, 2002, **43**, 3871-3874.
(40) Barluenga, J.; Mateos, C.; Aznar, F.; Valdes, C., *Org. Lett.*, 2002, **4**, 1971-1974.
(41) Ratni, H.; Kundig, E. P., *Org. Lett.*, 1999, **1**, 1997-1999.
(42) Ekegren, J. K.; Modin, S. A.; Alonso, D. A.; Andersson, P. G., *Tetrahedron: Asymmetry*, 2002, **13**, 447-449.
(43) Fernandez, F.; Garcia-Mera, X.; Vale, M. L. C.; Rodriguez-Borges, J. E., *Synlett.*, 2005, 319-321.
(44) Fernandez, F.; Garcia-Mera, X.; Rodriguez-Borges, J. E.; Vale, M. L. C., *Tetrahedron Lett.*, 2003, **44**, 431-433.
(45) Wang, Y. H.; Wilson, S. R., *Tetrahedron Lett.*, 1997, **38**, 4021-4024.
(46) Shou, W. G.; Yang, Y. Y.; Wang, Y. G., *Synthesis*, 2005, 530-536.
(47) Guo, H. C.; Wang, Z.; Ding, K. L., *Synthesis*, 2005, 1061-1068.
(48) Shi, M.; Cui, S. C.; Li, Q. H., *Tetrahedron*, 2004, **60**, 6163-6167.
(49) Shi, M.; Cui, S. C., *New. J. Chem.*, 2004, **28**, 1286-1288.
(50) Zulfiqar, F.; Kitazume, T., *Green Chem.*, 2000, **2**, 137-139.
(51) Loncaric, C.; Manabe, K.; Kobayashi, S., *Adv. Syn. Catal.*, 2003, **345**, 475-477.
(52) Akiyama, T.; Matsuda, K.; Fuchibe, K., *Synlett.*, 2002, 1898-1900.
(53) Whitesell, J. K., *Chem. Rev.*, 1989, **89**, 1581-1590.
(54) Kobayashi, S.; Komiyama, S.; Ishitani, H., *Angew. Chem., Int. Ed. Engl.*, 1998, **37**, 979-981.
(55) Kobayashi, S.; Kusakabe, K.; Komiyama, S.; Ishitani, H., *J. Org. Chem.*, 1999, **64**, 4220-4221.
(56) Kobayashi, S.; Kusakabe, K.; Ishitani, H., *Org. Lett.*, 2000, **2**, 1225-1227.
(57) Kobayashi, S.; Ueno, M.; Saito, S.; Mizuki, Y.; Ishitani, H.; Yamashita, Y., *PNAS*, 2004, **101**, 5476-5481.
(58) Yamashita, Y.; Mizuki, Y.; Kobayashi, S., *Tetrahedron Lett.*, 2005, **46**, 1803-1806.
(59) Timen, A. S.; Somfai, P., *J. Org. Chem.*, 2003, **68**, 9958-9963.
(60) Paugam, R.; Valenciennes, E.; Le Coz-Bardol, L.; Garde, J. C.; Wartski, L.; Lance, M.; Nierlich, M., *Tetrahedron: Asymmetry*, 2000, **11**, 2509-2523.
(61) Bromidge, S.; Wilson, P. C.; Whiting, A., *Tetrahedron Lett.*, 1998, **39**, 8905-8908.
(62) Bundu, A.; Guillarme, S.; Hannan, J.; Wan, H. L.; Whiting, A., *Tetrahedron Lett.*, 2003, **44**, 7849-7850.
(63) Guillarme, S.; Whiting, A., *Synlett.*, 2004, 711-713.

(64) Yao, S. L.; Johannsen, M.; Hazell, R. G.; Jorgensen, K. A., *Angew. Chem., Int. Ed. Engl.*, 1998, ***37***, 3121-3124.
(65) Akiyama, T.; Tamura, Y.; Itoh, J.; Morita, H.; Fuchibe, K., *Synlett.*, 2006, 141-143.
(66) Ishitani, H.; Kobayashi, S., *Tetrahedron Lett.*, 1996, ***37***, 7357-7360.
(67) Yao, S. L.; Saaby, S.; Hazell, R. G.; Jorgensen, K. A., *Chem.-Eur. J.*, 2000, ***6***, 2435-2448.
(68) Josephsohn, N. S.; Snapper, M. L.; Hoveyda, A. H., *J. Am. Chem. Soc.*, 2003, ***125***, 4018-4019.
(69) Mancheno, O. G.; Arrayas, R. G.; Carretero, J. C., *J. Am. Chem. Soc.*, 2004, ***126***, 456-457.
(70) Sunden, H.; Ibrahem, I.; Eriksson, L.; Cordova, A., *Angew. Chem., Int. Ed. Engl.*, 2005, ***44***, 4877-4880.
(71) Ishihara, K.; Yamamoto, H., *Eur. J. Org. Chem.*, 1999, 527-538.
(72) Thomas, S. E. *The Roles of Boron and Silicon*; OUP, 2003.
(73) Furuta, K.; Shimizu, S.; Miwa, Y.; Yamamoto, H., *J. Org. Chem.*, 1989, ***54***, 1481-1483.
(74) Ishihara, K.; Gao, Q. Z.; Yamamoto, H., *J. Am. Chem. Soc.*, 1993, ***115***, 10412-10413.
(75) Furuta, K.; Maruyama, T.; Yamamoto, H., *J. Am. Chem. Soc.*, 1991, ***113***, 1041-1042.
(76) Gao, Q. Z.; Maruyama, T.; Mouri, M.; Yamamoto, H., *J. Org. Chem.*, 1992, ***57***, 1951-1952.
(77) Marshall, J. M.; Palovich, M. R., *J. Org. Chem.*, 1998, ***63***, 4381-4384.
(78) Corey, E. J.; Bakshi, R. K.; Shibata, S., *J. Am. Chem. Soc.*, 1987, ***109***, 5551-5553.
(79) Corey, E. J.; Loh, T. P., *J. Am. Chem. Soc.*, 1991, ***113***, 8966-8967.
(80) Corey, E. J.; Guzmanperez, A.; Loh, T. P., *J. Am. Chem. Soc.*, 1994, ***116***, 3611-3612.
(81) Kiyooka, S.; Kaneko, Y.; Komura, M.; Matsuo, H.; Nakano, M., *J. Org. Chem.*, 1991, ***56***, 2276-2278.
(82) Kinugasa, M.; Harada, T.; Oku, A., *J. Org. Chem.*, 1996, ***61***, 6772-6773.
(83) Harada, T.; Yamauchi, T.; Adachi, S., *Synlett.*, 2005, 2151-2154.
(84) Corey, E. J.; Helal, C. J., *Angew. Chem., Int. Ed. Engl.*, 1998, ***37***, 1987-2012.
(85) Corey, E. J., *Angew. Chem., Int. Ed. Engl.*, 2002, ***41***, 1650-1667.
(86) Hayashi, Y.; Rohde, J. J.; Corey, E. J., *J. Am. Chem. Soc.*, 1996, ***118***, 5502-5503.
(87) Motoyama, Y.; Mikami, K., *J. Chem. Soc.-Chem. Commun.*, 1994, 1563-1564.
(88) Aggarwal, V. K.; Anderson, E.; Giles, R.; Zaparucha, A., *Tetrahedron: Asymmetry*, 1995, ***6***, 1301-1306.
(89) Futatsugi, K.; Yamamoto, H., *Angew. Chem., Int. Ed. Engl.*, 2005, ***44***, 1484-1487.
(90) Reilly, M.; Oh, T., *Tetrahedron Lett.*, 1995, ***36***, 221-224.
(91) Hawkins, J. M.; Loren, S., *J. Am. Chem. Soc.*, 1991, ***113***, 7794-7795.
(92) Hawkins, J. M.; Nambu, M.; Loren, S., *Org. Lett.*, 2003, ***5***, 4293-4295.
(93) Kelly, T. R.; Whiting, A.; Chandrakumar, N. S., *J. Am. Chem. Soc.*, 1986, ***108***, 3510-3512.
(94) Hattori, K.; Miyata, M.; Yamamoto, H., *J. Am. Chem. Soc.*, 1993, ***115***, 1151-1152.
(95) Ishihara, K.; Kuroki, Y.; Yamamoto, H., *Synlett*, 1995, 41-42.

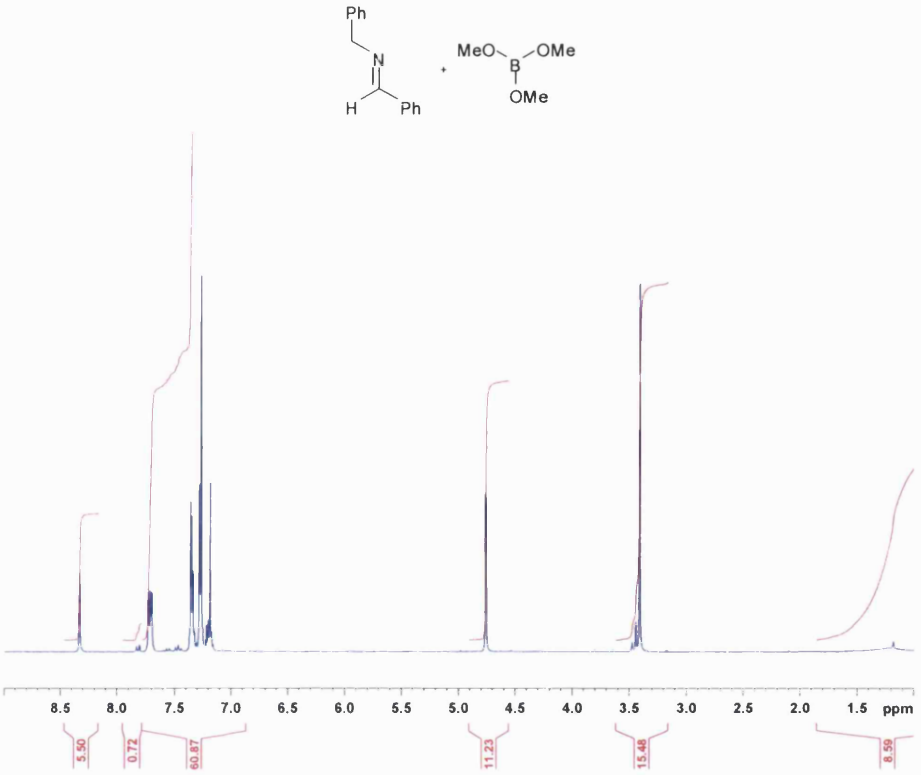
(96) Lock, R.; Waldmann, H., *Tetrahedron Lett.*, 1996, ***37***, 2753-2756.
(97) Yamada, H.; Kawate, T.; Matsumizu, M.; Nishida, A.; Yamaguchi, K.; Nakagawa, M., *J. Org. Chem.*, 1998, ***63***, 6348-6354.
(98) Ishihara, K.; Kurihara, H.; Yamamoto, H., *J. Am. Chem. Soc.*, 1996, ***118***, 3049-3050.
(99) Ishihara, K.; Kurihara, H.; Matsumoto, M.; Yamamoto, H., *J. Am. Chem. Soc.*, 1998, ***120***, 6920-6930.
(100) Thormeier, S.; Carboni, B.; Kaufmann, D. E., *J. Organomet. Chem.*, 2002, ***657***, 136-145.
(101) Sasai, H.; Suzuki, T.; Itoh, N.; Tanaka, K.; Date, T.; Okamura, K.; Shibasaki, M., *J. Am. Chem. Soc.*, 1993, ***115***, 10372-10373.
(102) Matsui, K.; Takizawa, S.; Sasai, H., *Tetrahedron Lett.*, 2005, ***46***, 1943-1946.
(103) Chong, J. M.; Shen, L. X.; Taylor, N. J., *J. Am. Chem. Soc.*, 2000, ***122***, 1822-1823.
(104) Chong, J. M.; Wu, T. R.; Shen, L. X., *Org. Lett.*, 2004, ***6***, 2701-2704.
(105) Umemoto, T.; Adachi, K., *J. Org. Chem.*, 1994, ***59***, 5692-5699.
(106) Lacour, J.; Hebbe-Viton, V., *Chem. Soc. Rev.*, 2003, ***32***, 373-382.
(107) Llewellyn, D. B.; Adamson, D.; Arndtsen, B. A., *Org. Lett.*, 2000, ***2***, 4165-4168.
(108) Zhou, Y.; Shan, Z. X., *Tetrahedron*, 2006, ***62***, 5692-5696.
(109) Antilla, J. C.; Wulff, W. D., *J. Am. Chem. Soc.*, 1999, ***121***, 5099-5100.
(110) Loncaric, C.; Wulff, W. D., *Org. Lett.*, 2001, ***3***, 3675-3678.
(111) Comins, D. L.; Joseph, S. P.; Goehring, R. R., *J. Am. Chem. Soc.*, 1994, ***116***, 4719-4728.
(112) Buonora, P.; Olsen, J. C.; Oh, T., *Tetrahedron*, 2001, ***57***, 6099-6138.
(113) Ishihara, K.; Miyata, M.; Hattori, K.; Tada, T.; Yamamoto, H., *J. Am. Chem. Soc.*, 1994, ***116***, 10520-10524.
(114) Childs, R. F.; Mulholland, D. L.; Nixon, A., *Can. J. Chem.*, 1982, ***60***, 801-808.
(115) Gutmann, V., *Coord. Chem. Rev.*, 1976, ***18***, 225-255.
(116) Lappert, M. F., *J. Chem. Soc.*, 1961, 817-822.
(117) Mayer, U.; Gutmann, V.; Gerger, W., *Monat. Chem.*, 1975, ***106***, 1235-1257.
(118) Beckett, M. A.; Brassington, D. S.; Coles, S. J.; Hursthouse, M. B., *Inorg. Chem. Commun.*, 2000, ***3***, 530-533.
(119) Beckett, M. A.; Strickland, G. C.; Holland, J. R.; Varma, K. S., *Polymer*, 1996, ***37***, 4629-4631.
(120) Perez-Fuertes, Y.; Kelly, A. M.; Johnson, A. L.; Arimori, S.; Bull, S. D.; James, T. D., *Org. Lett.*, 2006, ***8***, 2203-2203.
(121) Lu, G.; Li, X. S.; Chen, G.; Chan, W. L.; Chan, A. S. C., *Tetrahedron: Asymmetry*, 2003, ***14***, 449-452.
(122) Murahashi, S.; Imada, Y.; Kawakami, T.; Harada, K.; Yonemushi, Y.; Tomita, N., *J. Am. Chem. Soc.*, 2002, ***124***, 2888-2889.
(123) Yamashita, Y.; Ishitani, H.; Shimizu, H.; Kobayashi, S., *J. Am. Chem. Soc.*, 2002, ***124***, 3292-3302.
(124) Chen, Y.; Yekta, S.; Yudin, A. K., *Chem. Rev.*, 2003, ***103***, 3155-3211.
(125) Corminboeuf, O.; Renaud, P., *Org. Lett.*, 2002, ***4***, 1731-1733.
(126) Simonsen, K. B.; Gothelf, K. V.; Jorgensen, K. A., *J. Org. Chem.*, 1998, ***63***, 7536-7538.
(127) Kaufmann, D.; Boese, R., *Angew. Chem., Int. Ed. Engl.*, 1990, ***29***, 545-546.
(128) Sparks, S. M.; Chow, C. P.; Zhu, L.; Shea, K. J., *J. Org. Chem.*, 2004, ***69***, 3025-3035.

(129) Takamura, M.; Hamashima, Y.; Usuda, H.; Kanai, M.; Shibasaki, M., *Angew. Chem., Int. Ed. Engl.*, 2000, ***39***, 1650-1652.
(130) Onaka, M.; Ohno, R.; Yanagiya, N.; Izumi, Y., *Synlett*, 1993, 141-142.
(131) Braun, M.; Mai, B.; Ridder, D., *Eur. J. Org. Chem.*, 2001, 3155-3160.
(132) Hassan, N. A.; Bayer, E.; Jochims, J. C., *J. Chem. Soc., Perkin Trans. 1*, 1998, 3747-3757.
(133) Prasad, B. A. B.; Bisai, A.; Singh, V. K., *Tetrahedron Lett.*, 2004, ***45***, 9565-9567.
(134) Shi, Y.; Wulff, W. D.; Yap, G. P. A.; Rheingold, A. L., *Chem. Comm.*, 1996, 2601-2602.
(135) Ferris, J. P., *J. Org. Chem.*, 1962, ***27***, 2985-2990.
(136) Pilli, R. A.; Dias, L. C.; Maldaner, A. O., *J. Org. Chem.*, 1995, ***60***, 717-722.
(137) Lantos, I.; Razgaitis, C.; Vanhoeven, H.; Loev, B., *J. Org. Chem.*, 1977, ***42***, 228-231.
(138) Back, T. G.; Hamilton, M. D.; Lim, V. J. J.; Parvez, M., *J. Org. Chem.*, 2005, ***70***, 967-972.
(139) Corey, E. J.; Nicolaou, K. C.; Melvin, L. S., *J. Am. Chem. Soc.*, 1975, ***97***, 654-655.
(140) Barluenga, J.; Mateos, C.; Aznar, F.; Valdes, C., *J. Org. Chem.*, 2004, ***69***, 7114-7122.
(141) Ma, D. W.; Zhu, W., *Org. Lett.*, 2001, ***3***, 3927-3929.
(142) Davis, F. A.; Rao, A.; Carroll, P. J., *Org. Lett.*, 2003, ***5***, 3855-3857.
(143) Gracias, V.; Zeng, Y. B.; Desai, P.; Aube, J., *Org. Lett.*, 2003, ***5***, 4999-5001.
(144) Rosazza, J. P.; Bobbitt, J. M.; Schwarti.Ae, *J. Org. Chem.*, 1970, ***35***, 2564-2568.
(145) Hart, D. J.; Kanai, K., *J. Org. Chem.*, 1982, ***47***, 1555-1560.
(146) Comins, D. L.; Lamunyon, D. H., *J. Org. Chem.*, 1992, ***57***, 5807-5809.
(147) Chalard, P.; Remuson, R.; Gelas-Mialhe, Y.; Gramain, J. C., *Tetrahedron: Asymmetry*, 1998, ***9***, 4361-4368.
(148) Back, T. G.; Hamilton, M. D., *Org. Lett.*, 2002, ***4***, 1779-1781.
(149) Brown, J. D.; Foley, M. A.; Comins, D. L., *J. Am. Chem. Soc.*, 1988, ***110***, 7445-7447.
(150) Itoh, S.; Takada, N.; Ando, T.; Haranou, S.; Huang, X.; Uenoyama, Y.; Ohshiro, Y.; Komatsu, M.; Fukuzumi, S., *J. Org. Chem.*, 1997, ***62***, 5898-5907.
(151) Joly, G. D.; Jacobsen, E. N., *J. Am. Chem. Soc.*, 2004, ***126***, 4102-4103.
(152) Shoppee, C., *J. Chem. Soc.*, 1933, 37-45.
(153) Hoegy, S. E.; Mariano, P. S., *Tetrahedron*, 1997, ***53***, 5027-5046.
(154) Charette, A. B.; Boezio, A. A.; Janes, M. K., *Org. Lett.*, 2000, ***2***, 3777-3779.
(155) Quast, H.; Von Der Saal, W.; Stawitz, J., *Angew. Chem.*, 1981, ***93***, 619-620.
(156) Odonnell, M. J.; Bennett, W. D.; Bruder, W. A.; Jacobsen, W. N.; Knuth, K.; Leclef, B.; Polt, R. L.; Bordwell, F. G.; Mrozack, S. R.; Cripe, T. A., *J. Am. Chem. Soc.*, 1988, ***110***, 8520-8525.
(157) Curtin, N. J.; Barlow, H. C.; Bowman, K. J.; Calvert, A. H.; Davison, R.; Golding, B. T.; Huang, B.; Loughlin, P. J.; Newell, D. R.; Smith, P. G.; Griffin, R. J., *J. Med. Chem.*, 2004, ***47***, 4905-4922.
(158) Nicolaou, K. C.; Mathison, C. J. N.; Montagnon, T., *J. Am. Chem. Soc.*, 2004, ***126***, 5192-5201.
(159) Beak, P.; Payet, C. R., *J. Org. Chem.*, 1970, ***35***, 3281-3826.
(160) Tehrani, K. A.; NguyenVan, T.; Karikomi, M.; Rottiers, M.; De Kimpe, N., *Tetrahedron*, 2002, ***58***, 7145-7152.

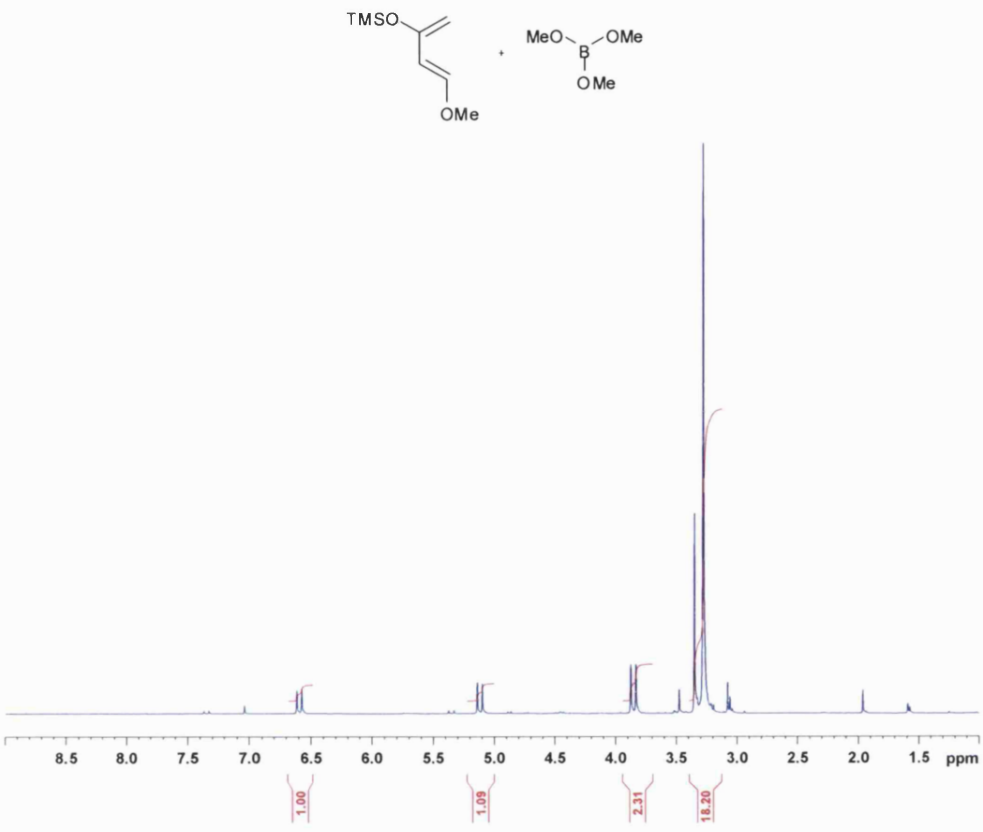
(161) Wang, C. J.; Delcros, J. G.; Cannon, L.; Konate, F.; Carias, H.; Biggerstaff, J.; Gardner, R. A.; Phanstiel, O., *J. Med. Chem.*, 2003, ***46***, 5129-5138.
(162) Mayer, M. F.; Hossain, M. M., *J. Org. Chem.*, 1998, ***63***, 6839-6844.
(163) Denis, J. N.; Fkyerat, A.; Gimbert, Y.; Coutterez, C.; Mantellier, P.; Jost, S.; Greene, A. E., *J. Chem. Soc., Perkin Trans. 1*, 1995, 1811-1815.
(164) Timmons, C.; Kattuboina, A.; McPherson, L.; Mills, J.; Li, G. G., *Tetrahedron*, 2005, ***61***, 11837-11842.
(165) Lingenfelter, D. S.; Helgeson, R. C.; Cram, D. J., *J. Org. Chem.*, 1981, ***46***, 393-406.
(166) Wu, T. R.; Shen, L. X.; Chong, J. M., *Org. Lett.*, 2004, ***6***, 2701-2704.
(167) Wang, X. W.; Adachi, S.; Iwai, H.; Takatsuki, H.; Fujita, K.; Kubo, M.; Oku, A.; Harada, T., *J. Org. Chem.*, 2003, ***68***, 10046-10057.

Appendix 1: NMR Spectra

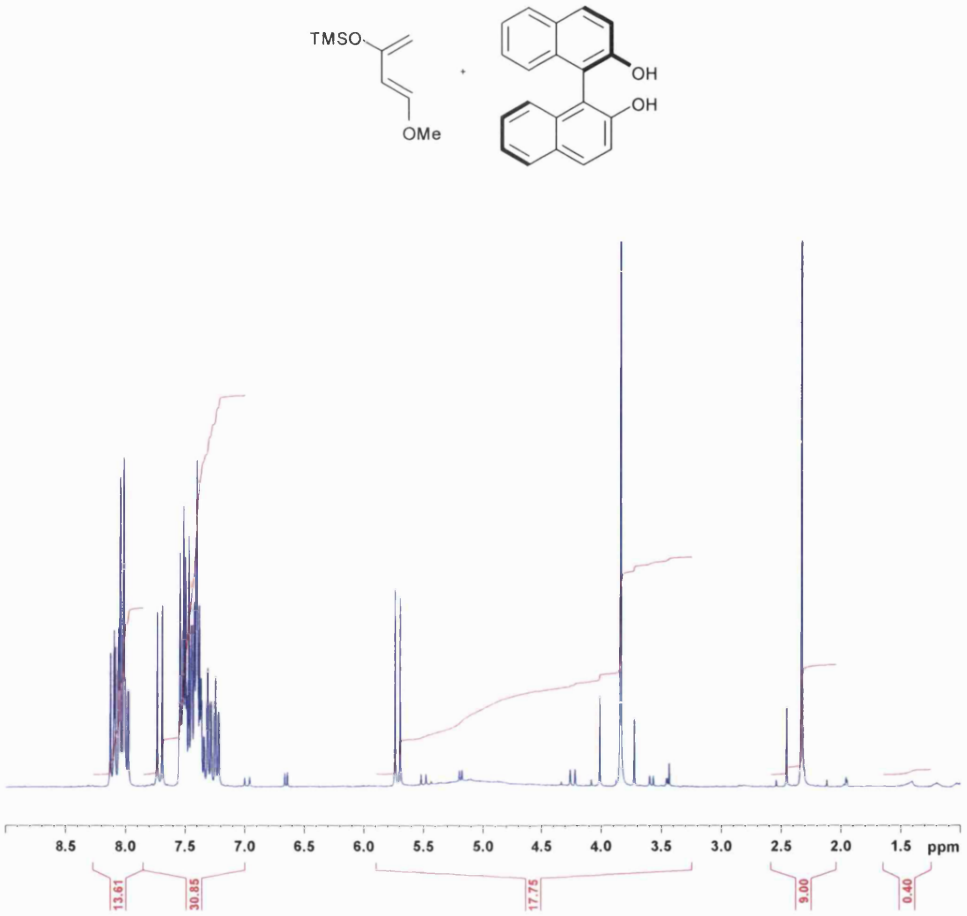
1.1 ^{1}H NMR spectrum of 1 eq. imine 42 mixed with 1 eq. $B(OMe)_3$ in $CDCl_3$



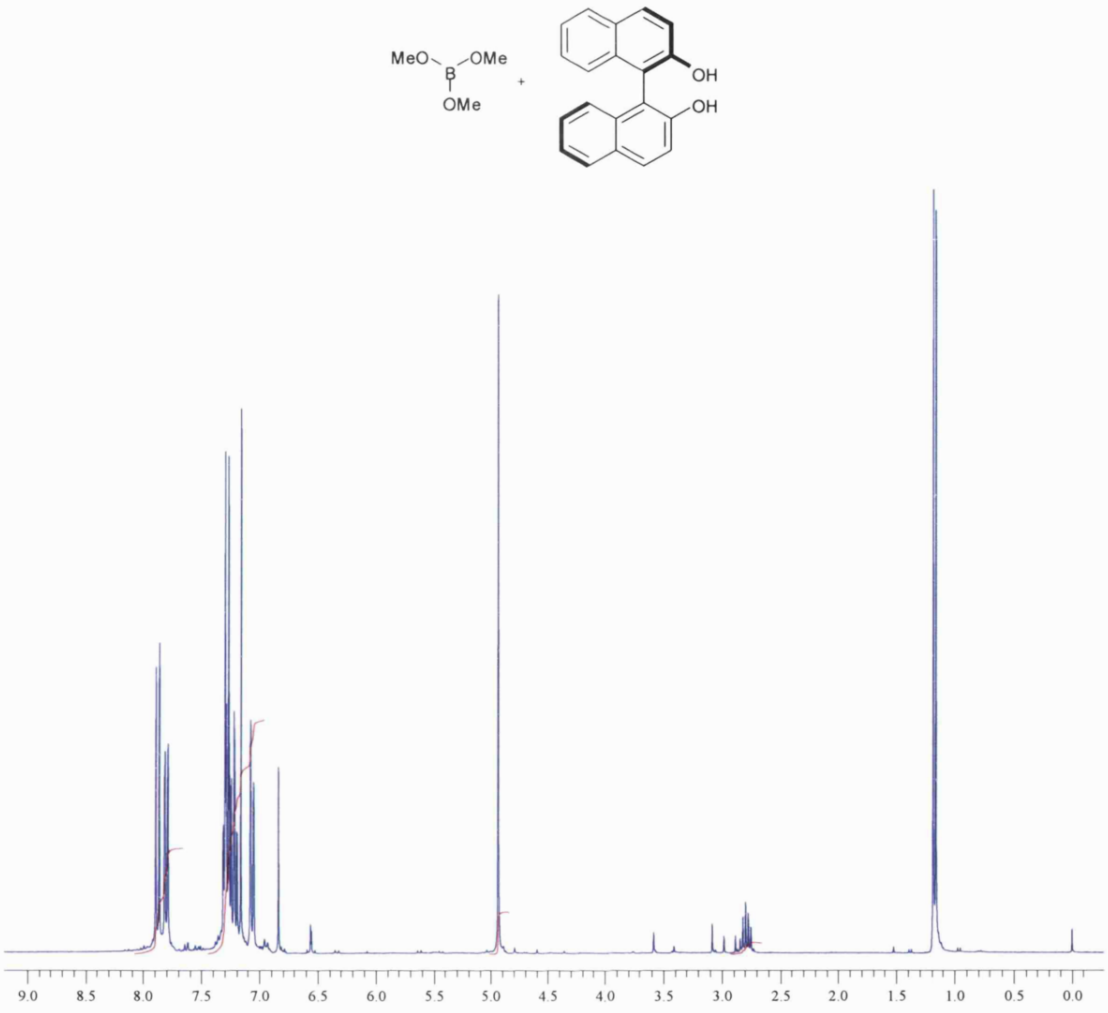
1.2 ^{1}H NMR spectrum of 1 eq. Danishefsky's Diene mixed with 1 eq. $B(OMe)_3$ in $CDCl_3$



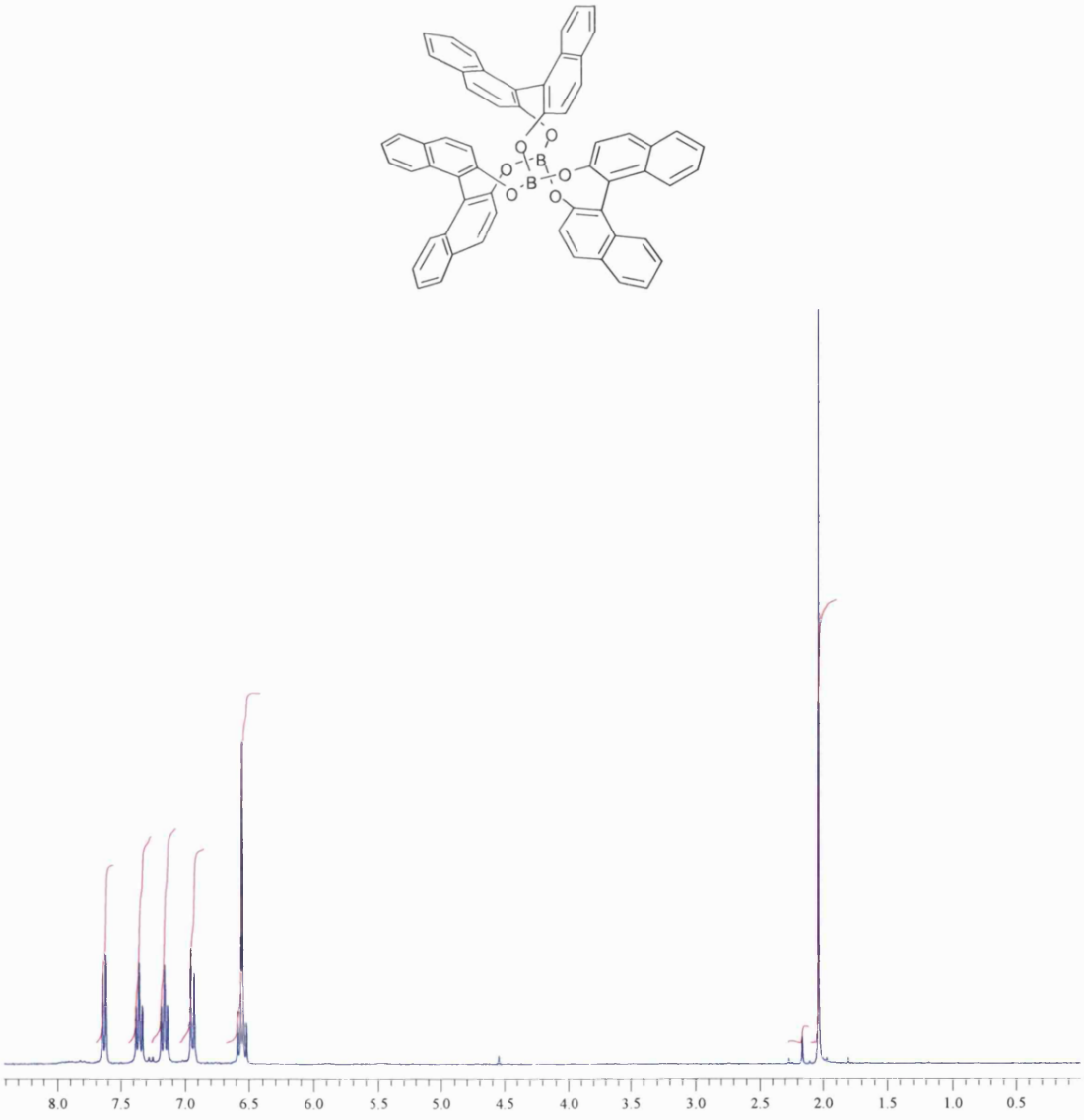
1.3 ^{1}H NMR spectrum of 1 eq. Danishefsky's Diene mixed with 1 eq. (*R*)-BINOL in $CDCl_3$



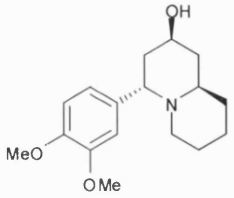
1.4 ^{1}H NMR spectrum of 1 eq. $B(OMe)_3$ mixed with 1 eq. (*R*)-BINOL in $CDCl_3$ for 1 h with 4Å molecular sieves (powdered)

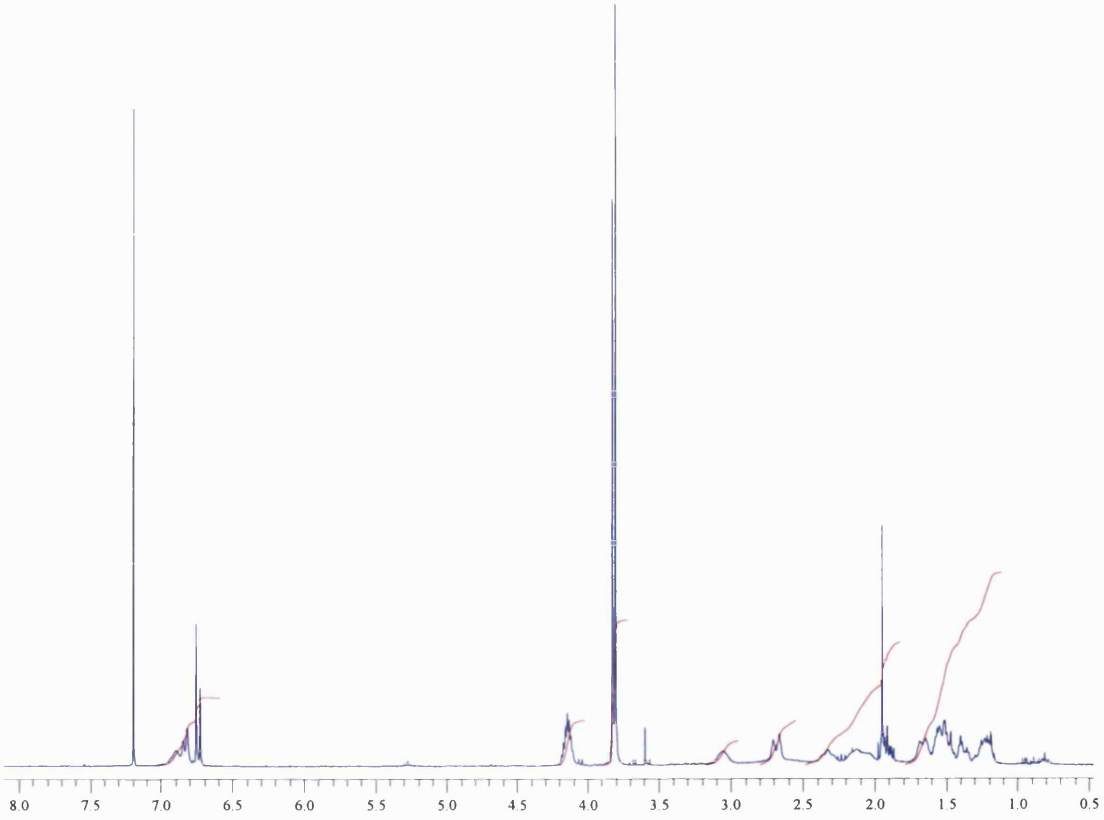


1.5 ^{1}H NMR spectrum propeller boronate 117 in $CDCl_3$

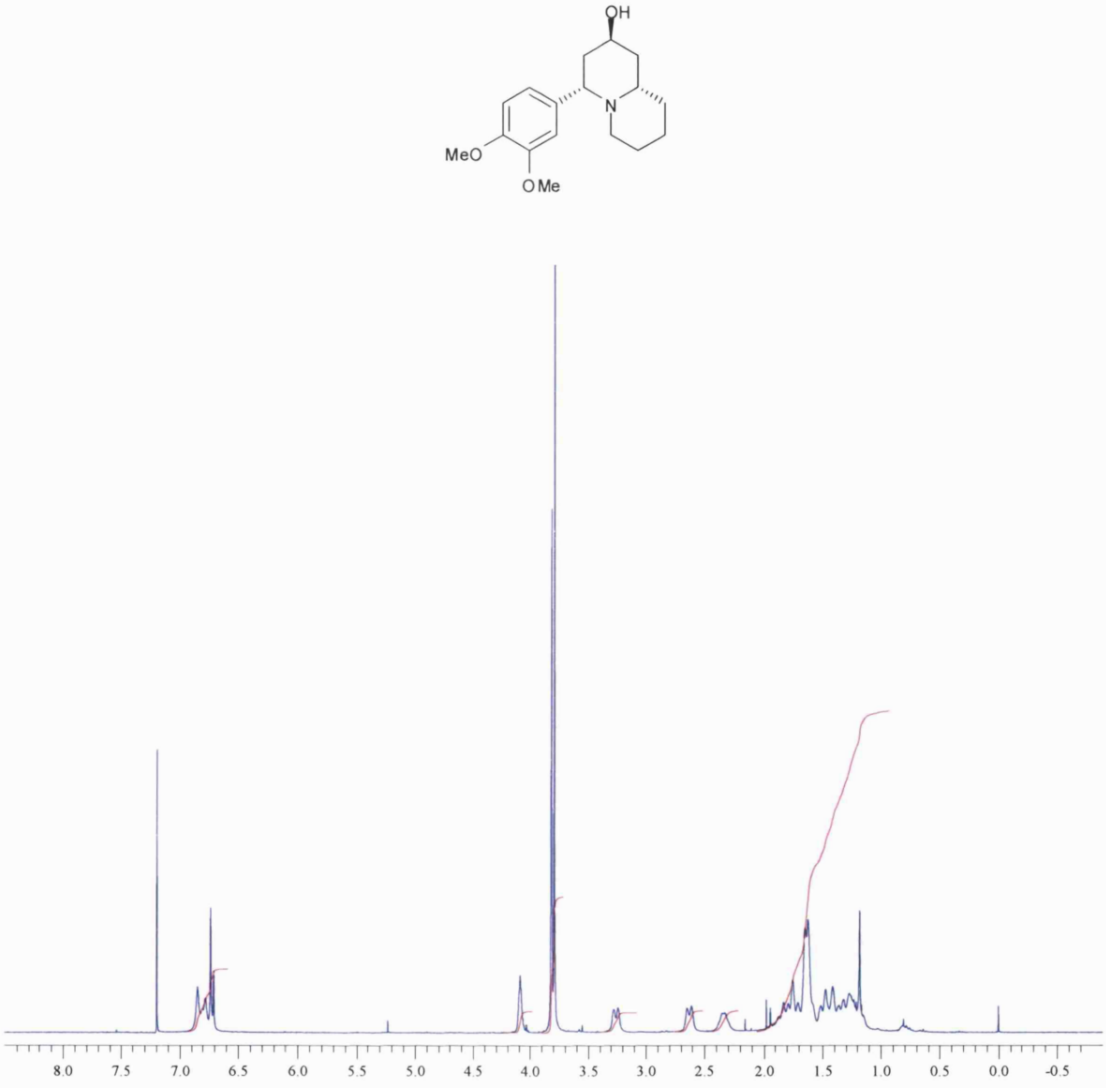


1.6 ^{1}H NMR spectrum of (-)-Lasubine (I) 199





1.7 ^{1}H NMR spectrum of (-)-Lasubine (II) 219



Appendix 2: X-ray crystal structure data for (*R*)-136

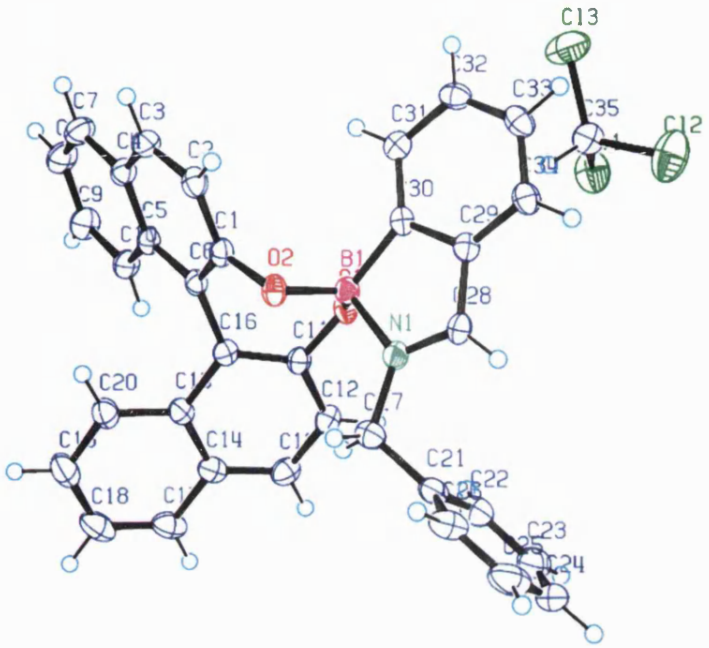


Table 1 Crystal data and structure refinement for k01tdj5.

Identification code	k01tdj5	
Empirical formula	C35 H25 B Cl3 N O2	
Formula weight	608.72	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1$	
Unit cell dimensions	a = 13.3810(2) Å	α= 90°.
	b = 8.02070(10) Å	β= 101.5600(10)°.
	c = 13.7581(2) Å	γ = 90°.
Volume	1446.64(4) Å^3	
Z	2	
Density (calculated)	1.397 Mg/m^3	
Absorption coefficient	0.352 mm^{-1}	
F(000)	628	
Crystal size	0.45 x 0.30 x 0.30 mm^3	
Theta range for data collection	3.67 to 27.49°.	
Index ranges	-17<=h<=17, -10<=k<=10, -17<=l<=17	
Reflections collected	29375	
Independent reflections	6620 [R(int) = 0.0438]	
Completeness to theta = 27.49°	99.4 %	
Absorption correction	None	
Max. and min. transmission	0.9019 and 0.8578	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6620 / 1 / 375	
Goodness-of-fit on F^2	1.025	
Final R indices [I>2sigma(I)]	R1 = 0.0404, wR2 = 0.1021	
R indices (all data)	R1 = 0.0457, wR2 = 0.1059	
Absolute structure parameter	0.03(5)	
Extinction coefficient	0.005(2)	
Largest diff. peak and hole	0.823 and -0.786 e.Å^{-3}	

Table 2 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for k01tdj5. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
B(1)	8604(2)	12242(3)	6785(2)	23(1)
N(1)	7974(1)	13537(2)	5954(1)	25(1)
O(1)	8144(1)	10620(2)	6501(1)	24(1)
O(2)	8538(1)	12800(2)	7770(1)	24(1)
C(1)	9726(1)	12588(2)	6555(1)	22(1)
C(2)	10673(2)	11874(3)	6887(1)	25(1)
C(3)	11518(2)	12429(3)	6514(2)	28(1)
C(4)	11420(2)	13696(3)	5811(2)	30(1)
C(5)	10476(2)	14437(3)	5463(2)	29(1)
C(6)	9642(1)	13865(3)	5840(1)	23(1)
C(7)	8582(2)	14382(3)	5532(1)	26(1)
C(8)	6848(2)	13703(3)	5727(2)	34(1)
C(9)	6474(1)	15340(3)	5256(2)	27(1)
C(10)	6049(2)	15433(3)	4248(2)	35(1)
C(11)	5704(2)	16964(4)	3829(2)	48(1)
C(12)	5781(2)	18383(4)	4414(2)	50(1)
C(13)	6194(2)	18280(3)	5416(2)	45(1)
C(14)	6542(2)	16771(3)	5826(2)	35(1)
C(101)	8413(2)	9406(2)	7211(1)	23(1)
C(102)	9068(2)	8111(3)	7026(2)	27(1)
C(103)	9381(2)	6919(3)	7730(2)	28(1)
C(104)	9076(2)	6975(2)	8660(2)	26(1)
C(105)	9462(2)	5815(3)	9422(2)	33(1)
C(106)	9179(2)	5898(3)	10320(2)	36(1)
C(107)	8484(2)	7121(3)	10488(2)	34(1)
C(108)	8097(2)	8269(3)	9775(2)	27(1)
C(109)	8386(1)	8244(2)	8833(1)	23(1)
C(110)	8031(1)	9458(2)	8073(1)	22(1)
C(201)	7665(1)	12481(2)	8119(1)	23(1)
C(202)	7124(2)	13856(3)	8389(2)	27(1)
C(203)	6234(2)	13623(3)	8716(2)	31(1)
C(204)	5824(2)	12001(3)	8747(1)	27(1)
C(205)	4860(2)	11745(3)	9014(2)	36(1)
C(206)	4433(2)	10185(4)	8969(2)	41(1)
C(207)	4957(2)	8816(3)	8675(2)	39(1)

C(208)	5903(2)	9008(3)	8446(2)	30(1)
C(209)	6368(2)	10608(3)	8484(1)	24(1)
C(210)	7350(1)	10861(2)	8228(1)	22(1)
C(1S)	12185(2)	16357(3)	7836(2)	37(1)
Cl(1S)	12220(1)	17794(1)	6893(1)	68(1)
Cl(2S)	12093(1)	17395(1)	8939(1)	54(1)
Cl(3S)	13242(1)	15032(1)	8045(1)	62(1)

Table 3 Bond lengths [Å] and angles [°] for k01tdj5

B(1)-O(2)	1.446(2)	C(102)-C(103)	1.366(3)
B(1)-O(1)	1.459(3)	C(103)-C(104)	1.420(3)
B(1)-C(1)	1.620(3)	C(104)-C(105)	1.419(3)
B(1)-N(1)	1.646(3)	C(104)-C(109)	1.426(3)
N(1)-C(7)	1.283(3)	C(105)-C(106)	1.364(3)
N(1)-C(8)	1.483(3)	C(106)-C(107)	1.402(3)
O(1)-C(101)	1.376(2)	C(107)-C(108)	1.369(3)
O(2)-C(201)	1.372(2)	C(108)-C(109)	1.425(3)
C(1)-C(2)	1.382(3)	C(109)-C(110)	1.437(3)
C(1)-C(6)	1.409(3)	C(110)-C(210)	1.490(3)
C(2)-C(3)	1.404(3)	C(201)-C(210)	1.384(3)
C(3)-C(4)	1.391(3)	C(201)-C(202)	1.410(3)
C(4)-C(5)	1.390(3)	C(202)-C(203)	1.368(3)
C(5)-C(6)	1.400(3)	C(203)-C(204)	1.416(3)
C(6)-C(7)	1.456(3)	C(204)-C(209)	1.419(3)
C(8)-C(9)	1.505(3)	C(204)-C(205)	1.426(3)
C(9)-C(14)	1.383(3)	C(205)-C(206)	1.372(4)
C(9)-C(10)	1.392(3)	C(206)-C(207)	1.405(4)
C(10)-C(11)	1.395(4)	C(207)-C(208)	1.372(3)
C(11)-C(12)	1.385(5)	C(208)-C(209)	1.423(3)
C(12)-C(13)	1.381(4)	C(209)-C(210)	1.442(3)
C(13)-C(14)	1.377(4)	C(1S)-Cl(1S)	1.743(3)
C(101)-C(110)	1.383(3)	C(1S)-Cl(3S)	1.746(3)
C(101)-C(102)	1.414(3)	C(1S)-Cl(2S)	1.757(2)
O(2)-B(1)-O(1)	115.20(16)	O(2)-B(1)-N(1)	109.69(16)
O(2)-B(1)-C(1)	111.31(16)	O(1)-B(1)-N(1)	104.29(15)
O(1)-B(1)-C(1)	117.24(17)	C(1)-B(1)-N(1)	96.97(14)

C(7)-N(1)-C(8)	124.53(17)	C(103)-C(104)-C(109)	119.04(18)
C(7)-N(1)-B(1)	111.41(16)	C(106)-C(105)-C(104)	120.7(2)
C(8)-N(1)-B(1)	124.06(15)	C(105)-C(106)-C(107)	119.8(2)
C(101)-O(1)-B(1)	113.84(14)	C(108)-C(107)-C(106)	121.4(2)
C(201)-O(2)-B(1)	119.04(15)	C(107)-C(108)-C(109)	120.6(2)
C(2)-C(1)-C(6)	118.17(17)	C(108)-C(109)-C(104)	117.64(18)
C(2)-C(1)-B(1)	133.55(17)	C(108)-C(109)-C(110)	122.80(18)
C(6)-C(1)-B(1)	108.25(16)	C(104)-C(109)-C(110)	119.54(17)
C(1)-C(2)-C(3)	120.01(19)	C(101)-C(110)-C(109)	118.59(18)
C(4)-C(3)-C(2)	120.93(18)	C(101)-C(110)-C(210)	119.14(17)
C(5)-C(4)-C(3)	120.35(18)	C(109)-C(110)-C(210)	121.98(16)
C(4)-C(5)-C(6)	117.97(19)	O(2)-C(201)-C(210)	120.83(17)
C(5)-C(6)-C(1)	122.58(18)	O(2)-C(201)-C(202)	117.67(17)
C(5)-C(6)-C(7)	127.00(18)	C(210)-C(201)-C(202)	121.47(17)
C(1)-C(6)-C(7)	110.31(16)	C(203)-C(202)-C(201)	120.48(19)
N(1)-C(7)-C(6)	112.74(18)	C(202)-C(203)-C(204)	120.22(19)
N(1)-C(8)-C(9)	113.91(17)	C(203)-C(204)-C(209)	119.63(18)
C(14)-C(9)-C(10)	119.2(2)	C(203)-C(204)-C(205)	121.0(2)
C(14)-C(9)-C(8)	120.15(19)	C(209)-C(204)-C(205)	119.3(2)
C(10)-C(9)-C(8)	120.6(2)	C(206)-C(205)-C(204)	120.6(2)
C(9)-C(10)-C(11)	119.6(2)	C(205)-C(206)-C(207)	119.9(2)
C(12)-C(11)-C(10)	120.2(2)	C(208)-C(207)-C(206)	121.0(2)
C(13)-C(12)-C(11)	119.9(2)	C(207)-C(208)-C(209)	120.6(2)
C(14)-C(13)-C(12)	119.8(3)	C(204)-C(209)-C(208)	118.47(18)
C(13)-C(14)-C(9)	121.3(2)	C(204)-C(209)-C(210)	119.41(18)
O(1)-C(101)-C(110)	119.93(17)	C(208)-C(209)-C(210)	122.07(19)
O(1)-C(101)-C(102)	118.39(17)	C(201)-C(210)-C(209)	118.10(17)
C(110)-C(101)-C(102)	121.67(18)	C(201)-C(210)-C(110)	119.02(17)
C(103)-C(102)-C(101)	119.99(18)	C(209)-C(210)-C(110)	122.88(17)
C(102)-C(103)-C(104)	120.91(19)	Cl(1S)-C(1S)-Cl(3S)	112.55(14)
C(105)-C(104)-C(103)	121.13(19)	Cl(1S)-C(1S)-Cl(2S)	110.28(14)
C(105)-C(104)-C(109)	119.82(19)	Cl(3S)-C(1S)-Cl(2S)	109.91(13)

Table 4 Anisotropic displacement parameters ($Å^2 x\ 10^3$)for k01tdj5. The anisotropic displacem takes the form: $-2\pi^2[\ h^2a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
B(1)	25(1)	23(1)	22(1)	4(1)	5(1)	-2(1)
N(1)	25(1)	24(1)	26(1)	3(1)	4(1)	-1(1)
O(1)	31(1)	23(1)	20(1)	1(1)	5(1)	-5(1)
O(2)	28(1)	23(1)	23(1)	-2(1)	10(1)	-5(1)
C(1)	27(1)	22(1)	17(1)	-2(1)	6(1)	-4(1)
C(2)	30(1)	24(1)	21(1)	-4(1)	4(1)	0(1)
C(3)	23(1)	32(1)	28(1)	-8(1)	4(1)	2(1)
C(4)	28(1)	36(1)	29(1)	-6(1)	11(1)	-6(1)
C(5)	31(1)	31(1)	25(1)	2(1)	10(1)	-4(1)
C(6)	27(1)	24(1)	20(1)	-1(1)	8(1)	-1(1)
C(7)	32(1)	22(1)	23(1)	4(1)	5(1)	-2(1)
C(8)	23(1)	37(1)	41(1)	8(1)	3(1)	-1(1)
C(9)	19(1)	35(1)	26(1)	4(1)	4(1)	-1(1)
C(10)	24(1)	51(1)	28(1)	0(1)	5(1)	4(1)
C(11)	26(1)	77(2)	38(1)	19(1)	3(1)	6(1)
C(12)	26(1)	45(2)	79(2)	27(1)	13(1)	8(1)
C(13)	29(1)	34(1)	73(2)	-4(1)	12(1)	1(1)
C(14)	26(1)	41(1)	38(1)	-4(1)	6(1)	-2(1)
C(101)	26(1)	21(1)	23(1)	0(1)	2(1)	-4(1)
C(102)	31(1)	25(1)	26(1)	-4(1)	8(1)	-4(1)
C(103)	27(1)	24(1)	34(1)	-4(1)	7(1)	2(1)
C(104)	26(1)	22(1)	29(1)	-1(1)	2(1)	-1(1)
C(105)	32(1)	28(1)	36(1)	4(1)	1(1)	6(1)
C(106)	41(1)	32(1)	33(1)	10(1)	0(1)	5(1)
C(107)	42(1)	35(1)	25(1)	8(1)	5(1)	1(1)
C(108)	31(1)	27(1)	24(1)	4(1)	5(1)	0(1)
C(109)	24(1)	20(1)	22(1)	0(1)	2(1)	-4(1)
C(110)	21(1)	20(1)	24(1)	-1(1)	2(1)	-4(1)
C(201)	26(1)	23(1)	21(1)	2(1)	5(1)	-1(1)
C(202)	34(1)	23(1)	27(1)	0(1)	8(1)	1(1)
C(203)	35(1)	30(1)	29(1)	2(1)	10(1)	7(1)
C(204)	25(1)	36(1)	21(1)	5(1)	5(1)	2(1)
C(205)	27(1)	50(1)	32(1)	4(1)	11(1)	6(1)
C(206)	25(1)	61(2)	40(1)	7(1)	11(1)	-4(1)
C(207)	32(1)	45(1)	41(1)	7(1)	8(1)	-12(1)

C(208)	30(1)	31(1)	31(1)	4(1)	7(1)	-5(1)
C(209)	24(1)	29(1)	20(1)	5(1)	3(1)	-2(1)
C(210)	25(1)	24(1)	17(1)	3(1)	4(1)	0(1)
Cl(1S)	101(1)	52(1)	50(1)	14(1)	16(1)	-3(1)
Cl(2S)	66(1)	50(1)	47(1)	-10(1)	16(1)	-11(1)
Cl(3S)	42(1)	42(1)	92(1)	-18(1)	-11(1)	9(1)